e-ISSN 2544-1620

Medical Science Pulse 2023 (17) 1

Original papers

Published online: 23 January 2023

DOI: 10.5604/01.3001.0016.2286

CRONKHITE-CANADA SYNDROME PRESENTING WITH LIFE-THREATENING PROTEIN-LOSING ENTEROPATHY: A CASE REPORT

Tolga Olmez[1 A-G]
• ORCID: 0000-0001-6145-6130

[1] Department of Gastrointestinal Surgery, University of Health Sciences, Adana City Training and Research Hospital, Adana, Turkey

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Cronkhite-Canada Syndrome (CCS) is a rare gastrointestinal (GI) polyposis syndrome. The diagnosis of CCS is made based on clinical, endoscopic, and histopathological findings. Common symptoms of CCS include chronic diarrhea, malnutrition, alopecia, skin hyperpigmentation, onychodystrophy, hypogeusia, and protein loss due to chronic inflammatory changes in the intestinal mucosa. Nutritional support, a high protein diet, antibiotics, correction of electrolyte imbalance, and corticosteroids are frequently used to treat CCS.

Aim of the study: Herein, we present a newly diagnosed CCS patient who has suffered life-threatening protein loss.

Material and methods: The patient's complete medical history was analyzed to fomulate this report.

Case report: A 62-year-old male patient presented with bloodless diarrhea, occurring 8-10 times per day for 4 months, and general malaise. On admission, arterial blood pressure was 80/50 mm/hg, pulse was 110 per minute and body temperature was 38.8°C. Laboratory tests highlighted a total protein of 38 mg/dL and albumin of 20 g/L. Upper and lower GI system (GIS) endoscopy revealed 2-20 mm polyps in the stomach, duodenum, and colon, and a small number in the distal esophagus. Pathological examination of polypectomy materials revealed edematous and inflamed lamina propria consisting of plasma cells, neutrophils, and eosinophils. The patient benefited from total parenteral nutrition, high protein dietary supplementation, and antibiotic therapy, and was followed with an upper and lower GIS endoscopy.

Conclusions: CCS is a rare disease that can cause life-threatening hypoalbuminemia and requires close follow-up.

KEYWORDS: Cronkhite-Canada Syndrome, hypoalbuminemia, gastrointestinal polyposis

Background

Cronkhite-Canada Syndrome (CCS) is a rare gastrointestinal (GI) polyposis syndrome first described in 1955 [1]. Although the etiology is unknown, fatigue and stress are often contributing factors, while other risk factors include surgery, pregnancy, radiotherapy, and alcohol use [2]. In addition, autoimmune diseases such as systemic lupus erythematosus, hypothyroidism, and rheumatoid arthritis may be accompanied [3,4].

The male to female ratio is 3:2 and CCS is often detected between the ages of 50-60 [5]. The dermatological triad is alopecia, skin hyperpigmentation, and onychodystrophy, although it is also characterized by chronic diarrhea, malnutrition, and protein loss due to chronic inflammatory changes in the intestinal mucosa [6-8].

Common presentations of CCS include hypogeusia (40.9%), diarrhea (35.4%), abdominal discomfort (9.1%), alopecia (8.2%), and xerostomia (6.4%), and the diagnosis is made by a combination of clinical, en-

doscopic and histopathological findings. Nutritional support, a high protein diet, antibiotics, correction of electrolyte imbalance, corticosteroids, proton pump inhibitors, 5-amino salicylate acid, antitumor necrosis factor α agents, and surgery are currently used in the treatment of CCS.

The risk of GI cancer may require aggressive screening of CCS patients. Given the numerous inflammatory types of polyps in CCS patients, it is nearly impossible to endoscopically detect malignant polyps or concomitant adenocarcinoma. Although a close relationship between CCS and cancer has not been demonstrated, the detectability of early-stage cancer is decreasing. In this case, patients present when the disease has moved beyond the early stage.

Aim of the study

This rare chronic disease leads to severe protein loss and malnutrition. In this article, we present a patient who presented with chronic malnutrition due to hypoalbuminemia and was diagnosed with CCS.

Material and methods

The medical documentation of a patient hospitalized in December 2019 in the Department of Gastroenterological Surgery at Koşuyolu Hıgh Specıalızatıon Educatıon and Research Hospıtal was used. The patient's consent for publication was obtained.

Case report

A 62-year-old male patient presented to our clinic with bloodless diarrhea and general malaise. The patient had diarrhea 8-10 times a day for 4 months, accompanied by weight loss of approximately 10%, intermittent abdominal pain, deterioration in taste, disfiguration in nail structure, and hair loss (Figure 1a-b). On admission, arterial blood pressure was 80/50 mm/hg, and pulse was 110 per minute. Physical examination of the abdomen was normal. Pretibial 3+ edema was present. Further examination of respiratory, neurological, and other systems were normal. He was diagnosed with hypothyroidism 3 months ago and was on daily L-thyroxine therapy. His TSH was 1.99 mIU/L (normal range 0.34-5.60 mIU/L), anti-thyroid microsomal antibodies were 139 IU/mL (normal range 0-34 IU/mL). It was also found that the patient had received eradication treatment for H. Pylori in their stomach 3 months ago. The patient and their family had no history of cancer or polyposis syndrome. The laboratory parameters of the patient on admission included leucocytes of $9700\times10^3/\mu L$ (normal range 4300-10300 $10^3/\mu L$), hemoglobin of 12.3 g/dL (normal range 11.1-17.1 g/dL), platelets of 240 $10^3/\mu L$ (normal range 140-440 $10^3/\mu L$), CRP of 158 mg/L (normal range 0-3.4 mg/L), blood urea nitrogen of 28 mg/dL (normal range 17-43 mg/dL), creatinine of 0.59 mg/dL (normal range 0.67-1,17 mg/dL), sodium of 143 mmol/L (normal range 136-146 mmol/L), potassium of 3.4 mmol/L (normal range 3.5-5.1 mmol/L), total protein of 38 mg/dL (normal range 64-83 mg/dL), and albumin of 20 g/L (normal range 35-52 g/L). On the first day of hospitalization, his body temperature was 38.8°C and possible fever etiologies were examined with blood, urine, and stool culture obtained, along with direct stool microscopy. The patient with protein-losing enteropathy first underwent empirical ceftriaxone 1×2 g and metronidazole 4×500 mg IV treatment after the initial fluid increase. Total parenteral nutrition and protein-rich oral diet were

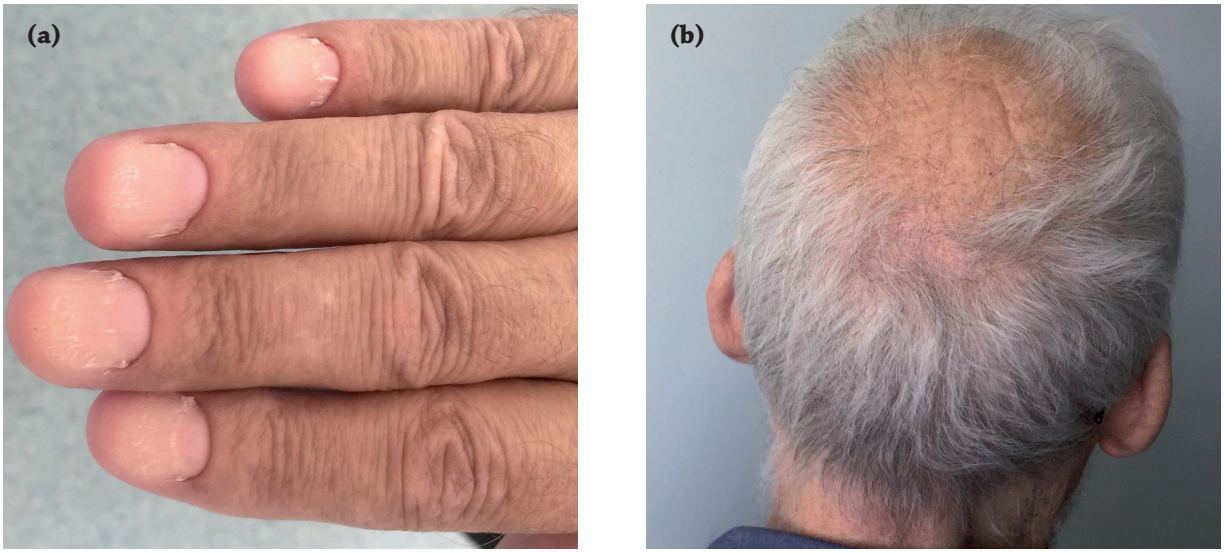

Figure 1. Clinical findings. (a) onychodystrophy in hand nails, (b) alopecia

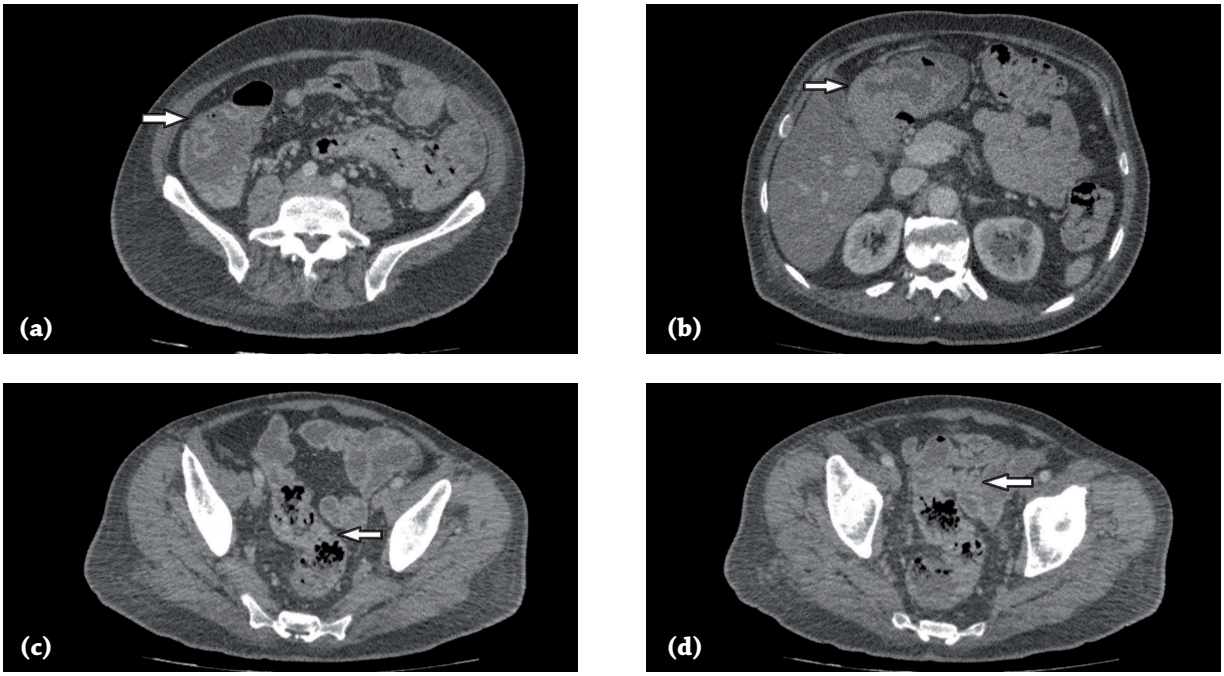

Figure 2. Abdominal CT shows folds in the stomach, small intestine, and colon mucosa: (a) right colon, (b) stomach, (c) rectum, (d) small intestine

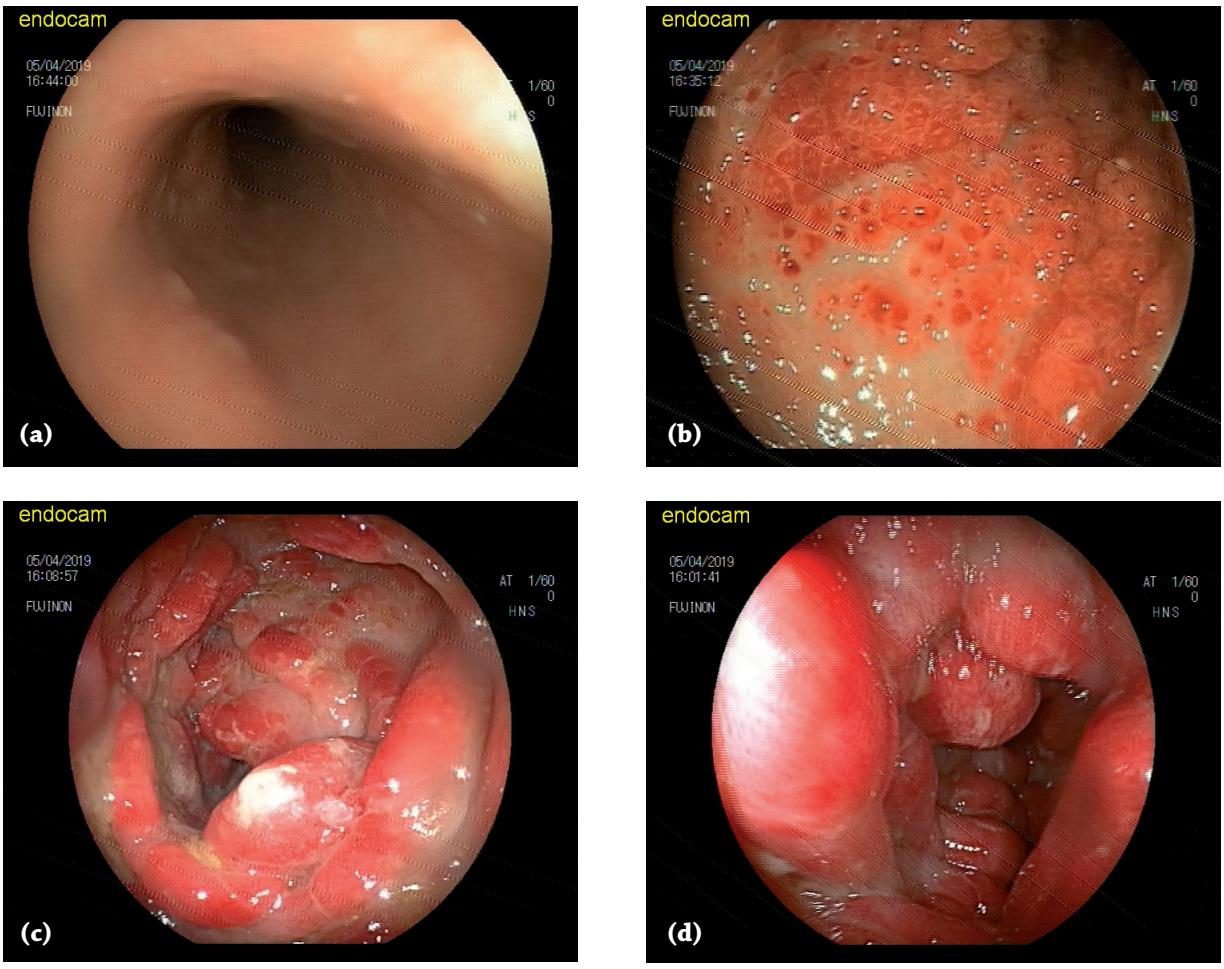

Figure 3. Upper-lower GIS endoscopy findings: (a) distal esophagus, (b) stomach-corpus, (c) sigmoid colon, (d) right colon

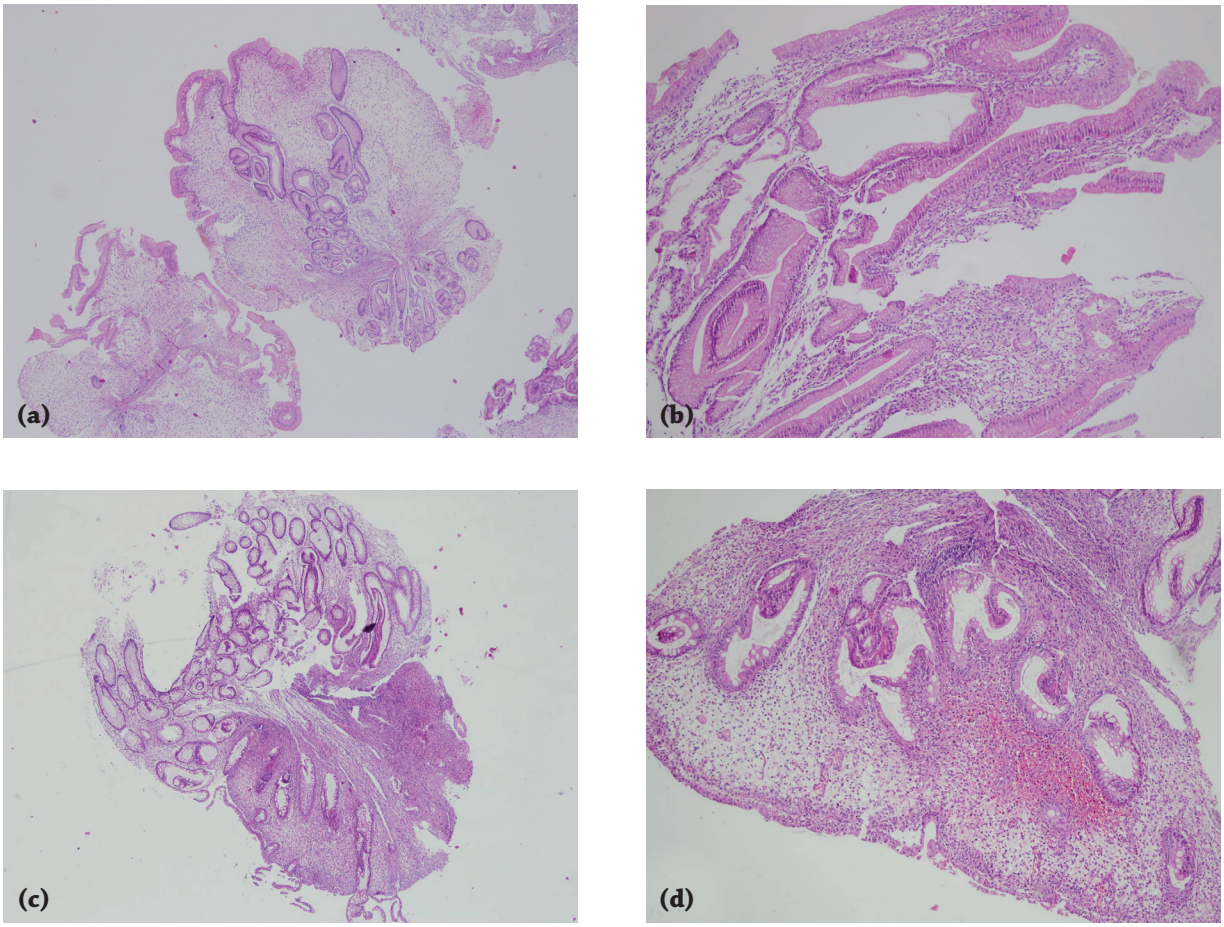

Figure 4. Pathological findings (a, b) infiltration of inflammatory cells in the gastric mucosa, edematous stroma, a dilated portion of the cystic enlarged branching foveolar epithelial polypoid tissues (a: hemotoxylin eosin staining, 40×; b: hemotoxylin eosin staining, 100×); (c, d) Polypoid tissues containing hyperplastic glands in an edematous stroma infiltrated with inflammatory cells in colon mucosa (c: hemotoxylin eosin staining, 40×; d: hemotoxylin eosin staining, 100×)

given to the patient as their oral nutrition was not sufficient to meet daily caloric needs. Abdominal computed tomography (CT) was performed and diffuse wall thickness was observed in the entire gastric and colon walls, and there was increased wall thickness in certain areas of the small intestine (Figure 2a-d). *Escherichia coli* and *Klebsiella oxytoca* were found in the blood culture, although there was no feature in other cultures or microscopy samples. The patient had no recurrent fever, the infection parameters regressed, and antibiotic treatment was continued for 10 days. Upper and lower GI system (GIS) endoscopy was performed in the patient whose oral nutrition increased and diarrhea decreased to 2-3 times a day. Colonoscopy showed multiple polyps of 2-20 mm along the entire colon, rectum, and terminal ileum mucosa. Likewise, gastroscopy revealed multiple 2-20 mm polypoid lesions across the entire stomach and 1st and 2nd segment of the duodenal mucosa, together with approximately 20 1-2 mm polypoid lesions in the distal esophagus (Figure 3a-d). Biopsy and polypectomy materials obtained from polyps revealed an edematous and inflamed lamina propria consisting of plasma cells, neutrophils, and eosinophils (Figure 4a-d).

The patients' antinuclear antibody was negative, total IgE was 291 IU/mL (normal range 0-100 IU/mL), carcinoembryonic antigen (CEA) was 3.5 (normal range 0-4 μg/L), CA19-9 was 28.1 U/mL (normal range 0-35 U/mL), anti-saccharomyces cerevisiae antibody (ASCA) was positive, and calprotectin was higher than the upper limit of the normal range. The patient was diagnosed with CCS after clinical, endoscopic, and pathological findings. After the treatment, GI symptoms improved, pretibial edema regressed, and oral nutrition was sufficient to maintain caloric intake. Informed consent was obtained from the patient, and they were followed up with upper GIS endoscopy and colonoscopy.

Discussion

CCS is a rare disease, with over 500 cases being reported since the day it was first identified, and 75% of these are from Japan [9]. The rare occurrence of

the syndrome makes it difficult to diagnose, and for this reason, in the health centers in which patients present initially, a polyposis syndrome such as familial adenomatosis polyposis (FAP) or inflammatory bowel diseases were also considered. Widespread polyps in both the stomach-duodenum and colon are typical for CCS. In addition, biopsies from these polyps showed typical features for the syndrome, including cystic dilated edematous hyperplastic glands in the stroma that contain lymphocytes, eosinophils, and neutrophils. Polypoid foveolar hyperplasia, and sporadic polyps (fundic gland polyps, adenomatous polyps) have similar morphological features in familial polyposis syndrome (Ménétrier disease, juvenile polyposis). The final diagnosis of CCS was based on clinical and laboratory findings. According to previous studies, this disease is common in men between the ages of 50-60 and is consistent with the data of our patient [10]. Dystrophic changes in nails, alopecia, and hyperpigmentation are the most characteristic triad observed on physical examination. Some patients have one or two of these findings. In our case, there was onychodystrophy with alopecia. In addition, hypogeusia, chronic diarrhea, abdominal pain, and xerostomia were present.

The treatments strategy of CSS currently includes corticosteroids, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, H2-receptor antagonists, hyperalimentation, cromolyn sodium, antibiotics, anabolic steroids, surgery, 5-aminosalicylate acid, antitumor necrosis factor α agents and the eradication of Helicobacter pylori, or a combination of these therapies [10-11]. Due to the present findings of our patient, we first achieved fluid-electrolyte balance and fed the patient with total parenteral nutrition in addition to oral nutrition. We applied antibiotic therapy because of bacterial growth in the peripheral venous blood which we thought was due to bacterial translocation. The patient benefited from this treatment protocol and did not relapse, while the parameters of infection regressed, and their symptoms improved. Since he had not received treatment for CSS before, we think that he benefited from supportive treatment, which was the first step, and antibiotics due to the infection detected in his blood. Recurrent attacks may require treatment such as corticosteroids, 5-amino salicylate acid, or antitumor necrosis factor α agents. Because the prognosis of CCS is poor, the 5-year mortality rate is 55% and the majority of mortality is associated with malnutrition, hypoalbuminemia, recurrent infection, sepsis, heart failure, and GI bleeding [12]. In addition, precancerous lesions and invasive carcinoma may develop among these polyps. Upon initial admission of the patient, no significant signs of GIS cancer were detected and a follow-up colonoscopy was performed. The relationship between CCS and cancer was found to be lower in patients with a reduction in the amount and size of polyps than in patients with no recurrence or no response [10].

Colonoscopy follow-up is also important for the detection of precancerous and invasive carcinomas. Esophageal polyps detected in our case are rare [3]. Close endoscopic and radiological follow-up would be performed to mitigate the risk of this disease which can affect all GIS components, including the small intestine.

Conclusions

CCS often presents with chronic diarrhea, abdominal pain, and hypoalbuminemia. However, it may turn into life-threatening malnutrition if not treated. The gold-standard treatment options include maintaining a fluid electrolyte balance and nutritional support. We also recommend close endoscopic follow-up to assess the activity of the disease and to remove premalignant lesions.

References

1. Cronkhite Jr. LW, Canada WJ. Generalized gastrointestinal polyposis: an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. N Engl J Med 1955;252: 1011-5.
2. Goto A. Cronkhite-Canada syndrome: epidemiological study of 110 cases reported in Japan. Nihon Geka Hokan 1995;64: 3-14.
3. Sweetser S, Ahlquist DA, Osborn NK, Sanderson SO, Smyrk TC, Chari ST, et al. Clinicopathologic features and treatment outcomes in Cronkhite-Canada syndrome: support for autoimmunity. Digestive Diseases and Sciences 2012;57: 496–502.
4. Kato K, Ishii Y, Mazaki T, Uehara T, Nakamura H, Kikuchi H, et al. Spontaneous regression of polyposis following abdominal colectomy and helicobacter pylori eradication for Cronkhite-Canada syndrome. Case Reports in Gastroenterology 2013;7:140–146.
5. Ward EM, Wolfsen HC. Review article: the non-inherited gastrointestinal polyposis syndromes. Aliment Pharmacol Ther 2002;16:333-342.
6. Elshout G, Dor FJ, Verhoog LC, Berk L, Vrijland WW. A Dutch patient presenting with a rare clinical syndrome. Gut 2011;60:1213. doi:10.1136/gut.2009.186080.
7. Slavik T, Montgomery EA. Cronkhite-Canada syndrome six decades on: the many faces of an enigmatic disease. J Clin Pathol 2014;67:891–7.
8. Seshadri D, Karagiorgos N, Hyser MJ. A case of Cronkhite-Canada syndrome and a review of gastrointestinal polyposis syndromes. Gastroenterol Hepatol 2012;8:197–201.

9. Matsui S, Kibi M, Anami E, Anami T, Inagaki Y, Kanouda A, et al. A case of Cronkhite-Canada syndrome with multiple colon adenomas and early colon cancers. Nihon Shokakibyo Gakkai Zasshi 2011;108:778-786.

10. Watanabe C, Komoto S, Tomita K, Hokari R, Tanaka M, Hirata I, et al. Endoscopic and clinical evaluation of treatment and prognosis of Cronkhite-Canada syndrome: a japanese nationwide survey. J Gastroenterol 2016;51:327-336. doi:10.1007/s00535-015-1107-7.

11. Ward EM, Wolfsen HC. Pharmacological management of Cronkhite-Canada syndrome. Expert Opin Pharmacother 2003;4:385-9.

12. Yun SH, Cho JW, Kim JW, Kim JK, Park MS, Lee NE, et al. Cronkhite-Canada syndrome associated with serrated adenoma and malignant polyp: a case report and a literature review of 13 Cronkhite-Canada syndrome cases in Korea. Clin Endosc 2013;463:301-305.

Word count: 1582 • Tables: 0 • Figures: 4 • References: 12

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Olmez T.
Cronkhite-Canada Syndrome Presenting with life-threatening protein-losing enteropathy: a case report.
Med Sci Pulse 2023;17(1):1–6. DOI: 10.5604/01.3001.0016.2286

Corresponding author:
Tolga Olmez
Email: tolgaolmez@gmail.com
University of Health Sciences, Adana City Training and Research Hospital, Adana, Turkey

Received: 17 October 2022
Reviewed: 16 January 2023
Accepted: 23 January 2023

e-ISSN 2544-1620

Medical Science Pulse 2023 (17) 1

Original papers

Published online: 24 January 2023

DOI: 10.5604/01.3001.0016.2314

PHYSICAL EXAMINATION IN NURSING RELATED TO WORK EXPERIENCE

Ewa Czeczelewska[1 A-F]
• ORCID: 0000-0002-4722-1682

Zuzanna Czeczelewska[2 B, D-F]
• ORCID: 0000-0002-3694-8819

[1] Faculty of Health Sciences, Academy of Applied Sciences Mazovia, Siedlce, Poland

[2] Faculty of Medicine, Medical University of Lublin, Poland

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Poland and other European countries have incorporated the physical assessment of patients into nursing practice. Appropriate practical skills and awareness of physical assessment play an important role in early diagnosis, appropriate management, and mitigation of adverse consequences resulting from the deterioration of the patient's health.

Aim of the study: The study aimed to evaluate the undertaking of physical examinations (PE) in professional practice by nurses with varying years of service.

Material and methods: The study included a group of 171 registered nurses from Poland. Using the author's non-standardized questionnaire, the study examined the professional experience and usefulness of PE in the nursing profession.

Results: Most nurses (56.3%) perform PE every day, regardless of seniority. The main reason for not performing PE was lack of time due to other nursing activities (32.7%) and insufficient staffing (29.9%). Some nurses also explained that it was due to the reluctance of medical personnel (24.1%). The most commonly used techniques in PE were inspection (44.1%) and palpation (32.8%). Most nurses (54.5%), regardless of seniority, felt satisfied with their PE performance. In the opinion of the respondents, 68.3% of patients approached PE undertaken by nurses with trust and appreciation, regardless of their seniority.

Conclusions: Professional experience did not significantly affect the perception and performance of PE by nurses in professional practice. In the opinion of the respondents, trust and appreciation was the reaction most often declared by patients concerning nurses undertaking PE, which had no statistically significant relationship with the seniority of the nurse.

KEYWORDS: nurse, physical examination, work experience, auscultation, palpation

Background

Advances in medical sciences, changes in the healthcare system, and the development of social awareness and expectations in the therapeutic field have contributed to the expansion of nurses' competencies. Therefore, European countries consider the ability to physically assess patients as a fundamental nursing skill [1]. As such, nurses need to acquire new skills to diagnose and treat patients [2]. Appropriate practical skills and awareness of physical assessment (PE) play an important role in early diagnosis, adequate management, and alleviation of adverse consequences resulting from the deterioration of the patient's health [1]. However, some studies have found that nurses do not perform PE of patients or only do so to a certain extent [3].

Aim of the study

The study aimed to evaluate PE undertaken in everyday professional practice by nurses with varying years of service.

Material and methods

Study design

The research was carried out under the project "We improve the qualifications of nurses and midwives" and was conducted in six voivodeships: Podlaskie, Warmińsko-Mazurskie, Lubelskie, Dolnośląskie, Kujawsko-Pomorskie, and Mazowieckie. The project was co-financed by the European Union from the 2014-2020 European Social Fund. Data were collected between October and November 2019.

Participants

This cross-sectional study included 500 nurses. The criterion for inclusion in the study was participation in a specialized course, "Interview and physical examination," implemented in the provinces of Lublin and Mazowieckie as part of the project "We improve the qualifications of nurses and midwives." After the conclusion of the specialist course, an online questionnaire was sent to all participants. Completing the questionnaire was tantamount to giving consent to participate in the study. Research material was collected from 171 participants, giving a response rate of 34.2%. The limited number of respondents was due to the small number of questionnaires returned and the inclusion of only correctly completed questionnaires.

Ethical considerations

According to the authors, pursuant to Article 37a of the Pharmaceutical Law Act (September 6, 2001, Journal of Laws of 2022, item 2301), the study did not require the opinion of the Bioethics Committee.

Data sources

The study used an original non-standardized questionnaire consisting of single and multiple-choice questions, which was validated at a medical center in the Mazovian Voivodeship. The questionnaire asked nurses about their work experience and PE performance. The first question concerned the usefulness of PE in the clinical practice of a nurse and whether it is performed by the nurse. When a negative answer was given, the respondents had to indicate the reasons for not carrying out the PE. The questions also enquired about the most commonly used techniques for PE and the systems and organs most often examined. In addition, the survey asked nurses how they perceived patient reactions to their physical assessment and how they feel when they discover abnormal findings during PE. The respondents filled in the questionnaire electronically.

Statistical methods

The answers were analyzed by dividing the respondents into one of four categories of work experience: <10 years, ≥10 years but <20 years, ≥20 but <30 years, and ≥30 years. Statistical analysis used a Chi-Squared (χ^2) test in the form of function G. The application of the function was due to the occurrence of numbers smaller than five in separate categories of work experience. The significance of the statistical test was set to $p \leq 0.05$.

Results

Characteristics of the study group

Figure 1 shows a numerical and percentage comparison of the number of respondents (n=171) in each year of service grouping. The most populous group (n=66, 38.6%) constituted nurses with work experience of ≥20 and <30 years, while the least populous was the group of nurses with <10 years (n=25, 14.6%) of practice. Those with the longest work experience (>30 years) constituted 28.7% (n=49) of respondents.

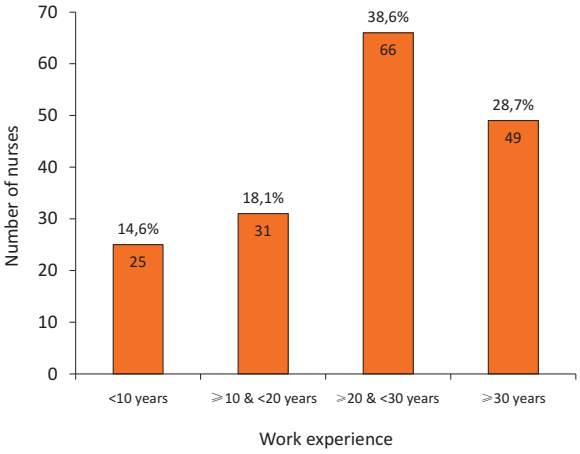

Figure 1. The number and percentage of nurses in specific categories of work experience (n=171)

Main results

The responses to the questions on the use of PE in everyday nursing practice are presented in Table 1 and are categorized based on length of service. Most nurses find it useful to perform PE (82.5%), though there were no significant differences ($p>0.05$) be-

Table 1. Responses to questions related physical examination in nursing categorized by work experience

Question	Categories	Work experience				p-value
		<10 years (n=25)	≥10 and <20 years (n=31)	≥20 and <30 years (n=66)	≥30 years (n=49)	
		Percentage (number)				
Do you think that knowledge and skills in the field of physical examination are useful in the nursing profession?	Yes.	80.0 (20)	72.4 (23)	87.7 (58)	89.8 (44)	0.853
	No.	4.0 (1)	12.9 (4)	3.1 (2)	0.0 (0)	
	Difficult to say.	16.0 (4)	12.9 (4)	9.2 (6)	10.2 (5)	
Do you perform physical examination in your professional practice?	Yes.	52.0 (13)	54.8 (17)	65.2 (43)	53.1 (26)	0.505
	No.	48.0 (12)	45.2 (14)	34.8 (23)	46.9 (23)	
If you selected "NO" in the previous question, what was the reason? You can select more than one answer.	No consent from patient.	0.0 (0)	9.5 (2)	5.0 (2)	0.0 (0)	0.695
	Reluctance on the part of doctors.	28.6 (6)	27.3 (6)	28.6 (14)	12.0 (3)	
	Reluctance on the part of nurses.	9.5 (2)	9.1 (2)	1.0 (4)	4.0 (1)	
	Lack of time due to performing other activities.	33.3 (7)	36.4 (8)	25.0 (10)	36.0 (9)	
	Lack of time due to insufficient staff.	28.6 (6)	18.2 (4)	25.0 (10)	48.0 (12)	
If you selected "YES" in the previous question, which techniques do you most often use during physical examinations? You can select more than one answer.	Inspection.	46.4 (13)	35.3 (12)	46.8 (37)	47.8 (22)	0.678
	Palpation.	35.7 (10)	29.4 (10)	29.1 (23)	37.0 (17)	
	Percussion.	3.6 (1)	8.8 (3)	3.8 (3)	0.0 (0)	
	Auscultation.	14.3 (4)	11.8 (4)	13.9 (11)	10.9 (5)	
	All aforementioned.	0.0 (0)	14.7 (5)	6.3 (5)	4.3 (2)	
Which systems or organs do you examine as part of your physical examination? You can give more than one answer.	Respiratory system – chest auscultation.	16.0 (12)	11.2 (11)	11.5 (25)	11.0 (16)	0.037
	Circulatory system – heart auscultation.	6.7 (5)	4.1 (4)	5.1 (11)	4.8 (7)	
	Nervous system – neurological reflexes.	2.7 (2)	6.1 (6)	3.2 (7)	4.8 (7)	
	Reproductive system.	2.7 (2)	4.6 (4)	3.2 (7)	2.7 (4)	
	Skeletal system.	6.7 (5)	7.1 (7)	4.6 (10)	8.9 (13)	
	Oral cavity.	16.0 (12)	12.2 (12)	15.7 (34)	17.1 (25)	
	Ear.	1.3 (1)	2.0 (2)	6.7 (14)	4.1 (6)	
	Eye.	5.8 (4)	9.2 (9)	7.4 (16)	6.2 (9)	
	Mammary gland.	1.3 (1)	4.1 (4)	4.6 (10)	2.7 (4)	
	Skin.	22.7 (17)	22.4 (22)	21.7 (47)	21.2 (31)	
	Lymph nodes.	6.7 (5)	6.1 (6)	3.2 (7)	2.7 (4)	
In your opinion, how do the patients react to the performance of physical examination by nurses?	Faith and appreciation.	64.0 (16)	71.0 (22)	60.6 (40)	77.6 (38)	0.745
	Reluctance and scepticism.	36.0 (9)	29.0 (9)	39.4 (26)	22.4 (11)	
How do you feel when you find an abnormality during the physical examination?	Satisfaction from possessed skills and acquiring new competences.	44.0 (11)	51.6 (16)	54.5 (36)	46.9 (23)	0.722
	Help and benefits for patient.	32.0 (8)	45.2 (14)	33.3 (22)	34.7 (17)	
	Professionalism.	24.0 (6)	3.2 (1)	12.1 (8)	18.4 (9)	

In questions with more than one answer possible, percentages in separate categories do not add up to 100.

tween the length of work experience and opinion on the usefulness of PE in clinical practice. However, the usefulness of PE was questioned by 16% of nurses with less than ten years of work experience, 12.9% with 10 to 20 years of work experience, and 10.2% of those with over 30 years of work experience. There were no significant statistical differences ($p>0.05$) in the undertaking of PE between the groups with different years of service.

The proportion of nurses who stated that they perform PEs in their daily practice was 56.3%, regardless of their work experience. The remaining 43.7% of the respondents indicated that the reasons for not doing PE were the reluctance of colleagues (24.1%), lack of time due to insufficient staff (29.9%), and a lack of time due to performing other nursing activities (32.7%). There were no significant statistical differences ($p>0.05$) between the reasons declared for not performing PEs between the work experience groups.

The most common techniques used during PE were inspection (44.1%) and palpation (32.8%), and the least frequently applied technique was percussion (4.1%). The organs examined most often during PE were the skin, which had a mean value of 22.1% across all work experience groups, and the oral cavity (15.3%). The least frequently examined were the mammary glands (3.2%) and reproductive system (3.3%). There were no statistically significant differences ($p>0.05$) between the most frequently used techniques or the most frequently examined organs between the specific work experience categories.

In the opinion of nurses across all work experience categories, 68.3% of patients responded to PE with faith and appreciation. The remaining patients (31.7%) reacted with reluctance and skepticism. The reactions of patients to PE performed by nurses did not vary significantly ($p>0.05$) between the different categories of work experience. Across all work experience categories, 48.3% of nurses indicated a feeling of satisfaction with their skills and acquiring new competencies while performing PE. On the other hand, a feeling of professionalism during PE was indicated by 24% of respondents with less than years of work experience and by 11.2% of respondents with more than years of service.

Discussion

The ability to perform a physical assessment is vital to the nursing process and is a core skill that all nurses must possess [1]. Regardless of their seniority, most nurses surveyed perceived PE as useful in clinical practice. Yamauchi (2001) found insignificant differences in the perception of PE as helpful in the nursing process in a study on nurses working in a regional hospital in Japan, in which respondents were divided into two groups by their length of service (up to 20 years and over 20 years) [4].

The professional experience of nurses contributes to the broadening of theoretical knowledge and improves practical skills in the health services field. Furthermore, the literature demonstrates that more experienced nurses are more skilled in the PE of patients. Indeed, respondents with less experience in nursing pointed out that physical assessment was a more difficult activity to perform [5]. This position was not confirmed by our research, as no significant differences were found between the undertaking of physical assessment and length of service. More than half of nurses, independent of their work experience, stated that they perform physical assesments in everyday practice. However, Mędrzycka-Dąbrowska et al. (2018) showed that work experience was a factor that significantly influenced PE performance in research conducted on 89 nurses working in selected hospital wards. Moreover, they found that such assessment was performed much more often by nurses with less professional work experience (between five and ten years) [6].

Research shows that nurses have difficulties in performing PEs. In particular, they pointed out the reluctance of colleagues, lack of time caused by insufficient staff, and lack of time due to performing other nursing activities as the reasons for such difficulties. Similar difficulties in performing PE were noted by Borowiak et al. (2021), who showed in a group of nurses that the most prevalent obstacles were low support from doctors (30.1%), other nurses (28.2%), and excessive duties (29.3%). Moreover, nurses with shorter work experience indicated a lack of a designated place and equipment to perform PEs more often than nurses with longer work experience [7]. Lijew et al. (2021) indicated that lack of time and breaks in work were barriers to the PE of patients by nurses working in an intensive care unit. In addition, the authors cited a lack of self-confidence, ward culture, and dependence on other technologies as barriers to PE [1].

Douglas et al. (2014) analyzed seven factors that make it difficult for nurses to perform a PE in a study on 434 registered emergency nurses in a large Australian clinical hospital. The factors included lack of time, too few breaks, reliance on other technologies, lack of faith, lack of nursing role models, no impact on patient care, ward culture, and area of specialization. However, the authors did not find a significant correlation between the barriers to performing PEs perceived by nurses and work experience [8]. The nurses with more than ten years of experience cited a lack of time, too few breaks, and a lack of self-confidence, whereas nurses with less than five years of practice indicated that a lack of nurse role models was a barrier.

The current study shows that the most frequently used PE techniques were inspection and palpation and the least used was percussion, which was used by less than 5% of respondents. There were no significant differences in the techniques used for PE between the groups based on work experience. Earlier studies also showed that percussion was the least frequently used technique during PE [9]. Cierzniakowska et al. (2021) stated in their research that nurses mainly assess a patient's health condition by examining their basic vital signs and using selected scales to assess their clinical condition and the risk of health deterioration. They found that nurses with more work experience performed PEs to a greater extent, and the differences resulting from length of service approached statistical significance (p=0.055) [10]. On the other hand, Cicolini et al. (2015) found no statistically significant differences in the quality or quantity of routine PEs by newly qualified nurses and nurses with more work experience in their study of 1182 Italian registered nurses [11].

The most frequently examined organs during PE were identified in this study as the skin and the oral cavity, while the least examined organs were the mammary glands and the reproductive system. The type of systems and organs examined by nurses during PE did not differ significantly based on their length of work experience. However, Mędrzycka-Dąbrowska et al. (2018) found that performing PE of the head, neck, and chest was related to work experience in their study [6]. In another study by Cierzniakowska et al. (2021), nurses stated that they possessed a good generalized sense of their skills and knowledge of PE, though they only used such skills to examine specific organs in their daily practice to a negligible extent [10].

The opinion of patients' is an objective indicator of a nurse's work [12]. Grabarska and Stefańska (2017) attempted to characterize a model of the modern nurse from the patient's perspective, and as many as 76% percent of patients declared faith in nurses [13]. In this regard, how nurses perceived the patient's opinions about their core competencies during PE was assessed in the current study. Regardless of their length of service, 68.3% of nurses perceived that patients reacted to PE with faith and appreciation. It is noteworthy, however, that a large percentage of patients (31.7%), in the opinion of nurses, reacted with reluctance and skepticism.

The determinants of creating professional satisfaction for nurses include the atmosphere in the workplace, the workplace itself, the company image, and the tasks performed [14]. PE is a new task that nurses are required to do, and it was found that nurses felt satisfied with their PE performance, regardless of their work experience. However, the proportion of nurses who thought their PE helped and benefited the patient was slightly lower (54.5% vs. 36.3%). Similar results were obtained by Czeczelewska (2021), who stated that the most satisfaction gained from learning new skills and competencies was felt by nurses from surgical wards (48.3%), primary health care (47.4%), and non-invasive treatment wards (33.8%). The feeling that nurses mentioned quite often when they found an abnormality during PE was that they were providing help and benefit to patients [9].

Limitations

The use of the author's non-standardized questionnaire could be considered a limitation of the research conducted. However, the scope of the survey is consistent with that of other research on PE in nursing. Therefore, the results of this study are an important contribution to the knowledge of the practical use of PE in nursing.

Conclusions

1. The length of work experience did not significantly affect the perception and performance of PE by nurses in professional practice.
2. The reasons for not conducting the physical examination by nurses, independent of their length of work experience were reluctance on the part of colleagues, a lack of time, and an excess of other nursing duties resulting from insufficient staffing.
3. No significant relationship was found between the length of work experience and the frequency of organs or systems examined during PE or in the techniques used during PE.
4. The majority of nurses felt faith and appreciation from the patient regarding PE and felt satisfied with their performance, irrespective of their length of work experience.

References

1. Liyew B, Tilahun AD, Kassew T. Practices and barriers towards physical assessment among nurses working in intensive care units: multicenter cross-sectional study. Biomed Res Int 2021; (78):1-12. https://doi.org/10.1155/2021/5524676.
2. Osborne S, Douglas C, Reid C, Jones L, Gardner G. The primacy of vital signs – acute care nurses' and midwives' use of physical assessment skills: a cross sectional study. Int J Nurs Stud 2015;52:951–62. https://doi.org/10.1016/J.IJNURSTU.2015.01.014.

3. Birks M, James A, Chung C, Cant R, Davis J. The teaching of physical assessment skills in pre-registration nursing programmes in Australia: issues for nursing education. Collegian 2014;21:245–53. https://doi.org/10.1016/J.COLEGN.2013.05.001.
4. Yamauchi T. Correlation between work experiences and physical assessment in Japan. Nurs Health Sci 2001;3:213–24. https://doi.org/10.1046/J.1442-2018.2001.00091.X.
5. Liyew B, Dejen Tilahun A, Kassew T. Knowledge, attitude, and associated factors towards physical assessment among nurses working in intensive care units: a multicenter cross-sectional study. Crit Care Res Pract 2020; (3):1-9. https://doi.org/10.1155/2020/9145105.
6. Mędrzycka-Dąbrowska W, Piotrkowska R, Kwiecień-Jaguś K, Jarzynkowski P, Popiołek S. Badanie fizykalne stosowane przez pielęgniarki na wybranych oddziałach szpitalnych. Med Rodz 2018; 21(1): 16-21. https://doi.org/10.25121/MR.2018.21.1.16. (In Polish).
7. Borowiak EJ, Bogus K, Glińska J. Kompleksowy wywiad i badanie fizykalne w praktyce pielęgniarskiej. Pielęgniarstwo w Opiece Długoterminowej 2021;5:283–96. https://doi.org/10.19251/PWOD/2020.4(3). (In Polish).
8. Douglas C, Osborne S, Reid C, Batch M, Hollingdrake O, Gardner G, et al. What factors influence nurses' assessment practices? Development of the barriers to nurses' use of physical assessment scale. J Adv Nurs 2014;70:2683–94. https://doi.org/10.1111/JAN.12408.
9. Czeczelewska EM. Badania fizykalne w praktyce pielęgniarskiej determinowane miejscem pracy. Pielęgniarstwo w Opiece Długoterminowej 2021;6:59–68. https://doi.org/10.19251/PWOD/2021.3(5). (In Polish).
10. Cierzniakowska K, Popow A, Kozłowska E, Kubiak J. Wykonywanie badań fizykalnych w zakresie kompetencji pielęgniarskich. [Performing physical examinations in the field of nursing competence]. Leczenie Ran 2021;18:1–7. https://doi.org/10.5114/LR.2021.104125. (In Polish).
11. Cicolini G, Tomietto M, Simonetti V, Comparcini D, Flacco ME, Carvello M, et al. Physical assessment techniques performed by Italian registered nurses: a quantitative survey. J Clin Nurs 2015;24:3700–6. https://doi.org/10.1111/JOCN.12997.
12. Jurkiewicz A, Kobos E. Opinia pacjentów na temat pracy pielęgniarek. Pielęgniarstwo Polskie 2017;65:473–80. https://doi.org/10.20883/pielpol.2017.64. (In Polish).
13. Grabska K, Stefańska W. Sylwetka zawodowa pielęgniarki w opinii pacjentów. [Figure of a professional nurse in patient opinions]. Problemy Pielęgniarstwa 2009;17:8–12. (In Polish).
14. Kunecka D. Determinanty satysfakcji zawodowej kadry pielęgniarskiej w Polsce. Zdrowie Publiczne i Zarządzanie 2016; 14 (1): 26–31. https://doi.org/10.4467/20842627OZ.16.004.5566. (In Polish).

Word count: 2232 • Tables: 1 • Figures: 1 • References: 14

Sources of funding:
The research was caried out under the project "We improve the qualifications of nurses and midwives" co-financed by European Union from the European Social Fund in the 2014-2020 perspective.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Czeczelewska E, Czeczelewska Z.
Physical examination in nursing related to work experience.
Med Sci Pulse 2023;17(1):7–12. DOI: 10.5604/01.3001.0016.2314

Correspondence author:
Ewa Czeczelewska
E-mail: eczeczelewska@mazovia.edu.pl
Academy of Applied Sciences Mazovia, Siedlce, Poland

Other authors/contact:
Zuzanna Czeczelewska
Email:z.czeczelewska@gmail.com

Received: 13 November 2022
Reviewed: 19 January 2023
Accepted: 24 January 2023

e-ISSN 2544-1620

Medical Science Pulse 2023 (17) 1

Original papers

Published online: 30 January 2023

DOI: 10.5604/01.3001.0016.2348

EVALUATION OF ANXIETY, DEPRESSION, AGGRESSION, AND LIFE SATISFACTION OF NURSES WORKING WITH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2-INFECTED PATIENTS

Elżbieta Szlenk-Czyczerska[1 A-G]
• ORCID 0000-0002-8145-6768

Marta Włodarczyk[2 A-G]
• ORCID 0000-0002-7847-9897

[1] Institute of Health Sciences, University of Opole, Poland

[2] Independent Public Health Care Institution MSWiA in Opole, Poland

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Negative emotions such as anxiety, depression, and aggression are among the factors that influence the level of perceived life satisfaction. Life satisfaction is related to physical and mental health and is an important component of human functioning. Nurses are particularly vulnerable to negative emotions due to their high-risk occupation and contact with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected individuals.

Aim of the study: The main objective of this study was to investigate the relationship between life satisfaction and levels of anxiety, depression, and aggression among nurses working with patients infected with the SARS-CoV-2 virus.

Material and methods: This cross-sectional observational study interviewed 110 individuals employed in two medical institutions in Opole and Lower Silesia Voivodeships between September and December 2021. Interviews were conducted using two standardized questionnaires, the Hospital Anxiety and Depression Scale-Modified Version (HADS-M) and the Satisfaction with Life Survey (SWLS).

Results: Analysis revealed that 26.3% (n=29) of nurses working with SARS-CoV-2-infected patients had marked anxiety symptoms, whereas 5.5% (n=6) of respondents had depressive disorders. There was no association between age and levels of anxiety (p=0.153) or depression (p=0.867), although the workplace had a significant effect on the severity of anxiety ($p<0.001$) and depressive symptoms (p=0.019). Most respondents (66.4%, n=73) described their life satisfaction as average. However, borderline depressive symptoms significantly impacted levels of perceived life satisfaction (p=0.031).

Conclusions: Nurses working in coronavirus disease (COVID) wards were more likely to show anxiety symptoms than signs of depression, while borderline depressive symptoms were more prevalent in those with low life satisfaction. Age and marital status did not affect the severity of anxiety or depression among respondents. These findings provide the basis for a deeper exploration of the issues and highlight the increasing need for more professional support.

KEYWORDS: anxiety, depression, satisfaction, nursing staff, and SARS-CoV-2 virus

Background

Work is an integral and essential area of daily life, and a well-organized professional activity can be a source of satisfaction and self-fulfillment, as well as a reason for discouragement and dissatisfaction. Nursing is already highly stressful due to the responsibility for human life [1-4] but working in a pandemic

environment is associated with added negative emotions such as anxiety and fear [5,6]. Sources of these emotions include inadequate staffing, long working hours, insufficient or inadequate personal protective equipment, isolation from family and friends for fear of infection, negative emotions and poor treatment from the public, lack of psychological support, and concern for patients [7,8]. Indeed, approximately one-third of nurses who worked during the coronavirus disease 19 (COVID-19) outbreak suffered from psychological symptoms [9]. Studies also clearly demonstrated a high prevalence of stress, anxiety, and depression among healthcare workers caring for COVID-19 patients [10,11]. These findings highlight the importance of comprehensive support strategies for caregivers and the need for further research to distinguish between psychological symptoms during and after an infectious disease outbreak [9].

Anxiety, depression, and aggression are among the factors that influence perceived life and work satisfaction levels [12,13], which are associated with an increased risk of occupational burnout [9]. It should be emphasized that life satisfaction in the nursing profession is very often related to job satisfaction and involves factors related to the individual characteristics of nurses and the work environment. Factors affecting the former include, among others, age, religion, marital status, self-esteem, adopted personality patterns, and burnout syndrome. Meanwhile, factors related to the work environment include relationships with medical staff, work organization, relationships with patients and their families, the scope and number of assigned tasks, motivational systems, in-house and external training courses, autonomy and prestige of the profession, workplace equipment, and compensation [14].

The COVID-19 pandemic affected nurses' mental health and well-being by exposing them to extremely stressful working conditions. However, there is limited research on the relationship between the COVID-19 pandemic and life satisfaction in nurses. Therefore, the topic was explored in-depth by examining the variables that may play a role.

Aim of the study

The primary study objective was to investigate the relationship between life satisfaction and symptoms of anxiety, depression, and aggression in nurses working with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients.

Material and methods

Study design and participants

This cross-sectional observational study was conducted between September and December 2021 on 110 subjects representing the nursing staff of two medical institutions in the Opole and Lower Silesia Voivodeships. The Research Ethics Committee of the University of Opole gave written consent for the study (Committee Opinion No. 32/2021). Inclusion criteria were nurses who worked with a SARS-CoV-2 -infected patient and consented to participate in the study by completing a paper-based questionnaire. Exclusion criteria included nurses who had no contact with a SARS-CoV-2-infected patient and did not consent to participate in the study.

Data collection

A total of 120 questionnaires were distributed and 110 correctly completed questionnaires were returned and qualified for further analysis. Levels of anxiety, depression, and aggression were assessed using the standardized Hospital Anxiety and Depression Scale Modified Version (HADS-M) questionnaire. Zigmond A. and Snaith R. authored the original questionnaire, while Majkowicz M.K., de Walden-Gałuszko, and Chojnacka-Szawłowska G. developed the Polish version. The questionnaire has two independent subscales for assessing anxiety and depression, with seven statements in each subscale and an additional two on irritability. Responses were calculated on a 4-point Likert scale (0-3), and the final score for each subscale ranged from 0-21 points. The questions on aggression ranged from 0-6 points, and scores of 0-7 indicated normal levels, scores of 8-10 indicated borderline levels, while scores in the range of 11-21 were considered abnormal [15].

The level of life satisfaction was assessed using the Satisfaction with Life Survey (SWLS) developed by Juczyński, which consists of five statements. The responses, recorded on a 7-point scale, ranged from completely dissatisfied (score of 1) to completely agree (score of 7). Summed scores ranged from 5 to 35, with a higher score indicating higher life satisfaction [16].

The self-reported questionnaire also contained questions on sociodemographics, including gender, age, education, place of residence, marital status, location, and length of time working in the profession.

Statistical analyses

Statistical analysis employed Microsoft Office 2019 (Microsoft Corporation, NM, USA), SPSS software (International Business Machines, NY, USA), and the R environment (version 3.6.0). Qualitative variables were expressed as a percentage, and variables expressed at the ordinal or nominal level were analyzed using tests based on the chi-squared distri-

bution. A continuity correction was applied to 2×2 tables, while tables larger than 2×2 had Fisher's exact test with extension applied. The significance level was set at p=0.05. Accordingly, p<0.05 indicated a significant relationship between the variables.

The smaller category, definite depressive symptoms, was removed to meet the conditions of the statistical test when examining the relationship between the severity of anxiety, depression, and aggression symptoms and the age of the respondents. Including the definite depressive symptoms category would have prevented the analysis.

Results

Sociodemographic characteristics of respondents

Females accounted for 94.5% (n=104) of respondents. The vast majority worked at the Healthcare Department of the Ministry of Interior and Administration hospital in Opole (72.7%, n=80), and those working at the hospital in Oława accounted for 27.3% (n=30) of respondents. The most common age groups were 31 to 40 years (31.8%, n=35) and over 50 years (28.2%, n=31). Most nurses had a Bachelor of Nursing degree (43.6%, n=48) or a Master of Nursing degree (29.1%, n=32). Meanwhile, the vast majority lived in the city (69.1%, n=76), and 65.5% (n=72) were in a relationship. Respondents were most likely to work in the Department of Internal Medicine (30%, n=33) or the Department of Surgery (29.1%, n=32). The seniority of the nurses was most commonly 0 to 5 years (24.5%, n=27) or over 30 years (24.5%, n=27) (Table 1).

Table 1. Sociodemographic data of the study group (n=110)

Variable	Categories	n	%
Hospital	In Opole	80	72.7
	In Oława	30	27.3
Gender	Female	104	94.5
	Male	6	5.5
Age	20-30 years	22	20.0
	31-40 years	35	31.8
	41-50 years	22	20.0
	Over 50 years	31	28.2
Education	Secondary school or medical school	30	27.3
	BA	48	43.6
	MA	32	29.1
Place of residence	Urban	76	69.1
	Rural	34	30.9
Marital status	In a relationship	72	65.5
	Not in a relationship	38	34.5
Place of work	Department of Internal Medicine	33	30.0
	Department of Surgery	32	29.1
	Department of Anesthesiology and Critical Care	20	18.2
	Other	25	22.7
Seniority in the profession (in years)	0-5	27	24.5
	6-10	10	9.1
	11-15	15	13.6
	16-20	17	15.5
	21-25	4	3.6
	26-30	10	9.1
	Over 30	27	24.5

Legend: BA – bachelor's degree; MA – master's degree; n – group quantity; % – percentage.

Assessment of anxiety, depression, aggression, and life satisfaction

Table 2 provides statistical data on life satisfaction and the prevalence of anxiety, depression, and aggression among nurses working in COVID wards. The overall anxiety prevalence score yielded a mean score of 8.00 (minimum=0.00 and maximum=19.00), and the mean HADS-M anxiety subscale score was 8.34. The median HADS-M depression subscale score was 4.50 (minimum=0.00 and maximum=13.00), while the mean subscale score was 4.79. Analysis of the aggression variable revealed a median HADS-M aggression subscale score of 4.00 (minimum=0.00 and maximum=6.00) and a mean subscale score of 3.49. In addition, 100% of respondents had a normal HADS-M aggression score. The mean life satisfaction was 22.00 (minimum=8.00 and maximum=35.00), with a mean score of 21.51 on the SWLS scale (Table 2).

Table 2. Assessment of anxiety, depression, aggression, and life satisfaction in nurses (n=110)

Variable	M	SD	Min	Max	Q25	Me	Q75
HADS-M Anxiety	8.34	3.87	0.00	19.00	6.00	8.00	11.00
HADS-M Depression	4.79	3.56	0.00	13.00	1.25	4.50	8.00
HADS-M Aggression	3.49	1.43	0.00	6.00	2.00	4.00	4.00
SWLS Score	21.51	6.20	8.00	35.00	17.25	22.00	25.00
SWLS Score	5.77	2.19	1.00	10.00	4.25	6.00	7.00

Legend: HADS-M – Hospital Anxiety and Depression Scale Modified Version; Max – maximum; M – mean; Me – median; Min – minimum; Q25% – first quartile; Q75% – third quartile; SD – standard deviation; SWLS – Satisfaction with Life Survey.

A detailed analysis of anxiety, depression, and aggression prevalence among COVID ward staff re-

vealed no anxiety symptoms in 38.2% (n=42), borderline anxiety symptoms in 35.5% (n=39), and significant anxiety symptoms in 26.3% (n=29) of respondents. There were no depressive symptoms observed in 72.7% (n=80), borderline depressive symptoms observed in 21.8% (n=24), and marked depressive symptoms in 5.5% (n=6) of respondents. Analysis of aggression was not possible, as 100% of respondents had a normal score.

Analysis of the HADS-M anxiety and depression subscales showed no effect in the HADS-M anxiety subscale (p=0.283). In contrast, the HADS-M depression subscale showed that the distribution of responses was significantly different from that in which the proportion would have been 1 (p=0.00) (Table 3).

Life satisfaction was high in 16.3% (n=18) of the respondents, 66.4% (n=73) had a medium level of life satisfaction, and 17.3% (n=19) had a low level of life satisfaction. The analysis revealed that respondents were significantly more likely to have an average level of life satisfaction (p=0.001) (Table 3).

Table 3. Assessment of anxiety and depression severity and life satisfaction among nurses working in coronavirus disease wards. Data include the distribution of responses and chi-squared test scores for one sample (n=110)

Variable		n	%
HADS-M Anxiety	Normal	42	38.2
	Borderline anxiety symptoms	39	35.5
	Prominent anxiety symptoms	29	26.3
HADS-M Depression	Normal	80	72.7
	Borderline depression symptoms	24	21.8
	Prominent depression symptoms	6	5.5

Variable	Categories	Values	n	Proportion	Residuals	Chi² test
HADS-M Anxiety	**Normal**	Observed	42.00	0.382	–5.33	χ^2=2.53 df=2 p=0.283
		Expected	36.67	0.333		
	Borderline anxiety symptoms	Observed	39.00	0.355	–2.33	
		Expected	36.67	0.333		
	Prominent anxiety symptoms	Observed	29.00	0.263	7.67	
		Expected	36.67	0.333		
HADS-M Depression	**Normal**	Observed	80.00	0.727	–43.33	χ^2=81.24 df=2 p=0.00
		Expected	36.67	0.333		
	Borderline depression symptoms	Observed	24.00	0.218	12.67	
		Expected	36.67	0.333		
	Prominent depression symptoms	Observed	6.00	0.055	30.67	
		Expected	36.67	0.333		
Satisfaction with life according to SWLS	**Low**	Observed	19.00	0.173	17.67	χ^2=54.02 df=2 p=0.001
		Expected	36.67	0.333		
	Average	Observed	73.00	0.664	–36.33	
		Expected	36.67	0.333		
	High	Observed	18.00	0.163	18.67	
		Expected	36.67	0.333		

Legend: Chi²/χ^2 – chi-squared; df – degrees of freedom; HADS-M – Hospital Anxiety and Depression Scale Modified Version; n – group quantity; p – statistical significance; % – percentage; SWLS – Satisfaction with Life Survey.

Relationship between severity of symptoms of anxiety and depression and life satisfaction and age of caregivers working with severe acute respiratory syndrome coronavirus 2-infected patients

Analysis of the relationship between anxiety symptom severity and age showed borderline anxiety symptoms in 40.9% (n=9) of subjects aged 20 to 30 years, 22.9% (n=8) aged 31 to 40 years, 27.3% (n=6) aged 41 to 50 years, and 51.6% (n=16) aged over 50 years. Pronounced anxiety symptoms were present in 18.2% (n=4) of participants aged 20 to 30 years, 28.6% (n=10) aged 31 to 40 years, 27.3% (n=6) aged 41 to 50 years, and 29% (n=9) aged over 50 years. However, there was no significant association between anxiety symptom severity and respondent age (p=0.153). Likewise, there was no relationship be-

tween the severity of depressive symptoms and age (p=0.867), which were reported by 28.6% (n=6) of respondents aged 20 to 30 years, 20.6% (n=7) aged 31 to 40 years, 19% (n=4) aged 41 to 50 years, and 25% (n=7) aged over 50 years (Table 4).

Analysis of the relationship between life satisfaction level and age showed that respondents aged 20 to 30 years (72.7%, n=16) were the most satisfied with their lives. Life satisfaction was also high in those aged 31 to 40 years (57.1%, n=20), 41 to 50 years (77.3%, n=17), and over 50 years (64.5%, n=20). However, there was no significant association between life satisfaction and the age of nurses working with SARS-CoV-2-infected patients (p=0.406) (Table 4).

Table 4. Assessment of the association between the severity of anxiety and depression symptoms and life satisfaction and age of nurses working with severe acute respiratory syndrome coronavirus 2-infected patients (n=110)

Variable			Age (in years)				Chi² test
			20–30	31–40	41–50	over 50	
HADS-M Anxiety	Normal	n	9	17	10	6	χ^2=9.378 df=6 p=0.153
		%	40.9	48.6	45.5	19.4	
	Borderline anxiety symptoms	n	9	8	6	16	
		%	40.9	22.9	27.3	51.6	
	Prominent anxiety symptoms	n	4	10	6	9	
		%	18.2	28.6	27.3	29	
Total		n	22	35	22	31	
		%	100	100	100	100	
HADS-M Depression	Normal	n	15	27	17	21	χ^2=0.726 df=3 p=0.867
		%	71.4	79.4	81	75	
	Borderline depression symptoms	n	6	7	4	7	
		%	28.6	20.6	19	25	
Total		n	21	34	21	28	
		%	100	100	100	100	
Satisfaction with life	Low	n	5	6	2	6	χ^2=6.152 df=6 p=0.406
		%	22.7	17.1	9.1	19.4	
	Average	n	16	20	17	20	
		%	72.7	57.1	77.3	64.5	
	High	n	1	9	3	5	
		%	4.5	25.7	13.6	16.1	
Total		n	22	35	22	31	
		%	100	100	100	100	

Legend: Chi²/χ^2 – chi-squared; df – degrees of freedom; HADS-M – Hospital Anxiety and Depression Scale Modified Version; n – group quantity; p – statistical significance; % – percentage.

Relationship between severity of anxiety and depressive symptoms and life satisfaction and marital status of nurses working in coronavirus disease wards

Significant anxiety symptoms were observed in 33.3% (n=24) of those in a relationship and 13.2% (n=5) of those not in a relationship, while there were no anxiety symptoms in 31.9% of those in a relationship and 50.0% of those not in a relationship. There was no significant association between the severity of anxiety symptoms and the marital status of caregivers working in COVID wards (p=0.050). When analyzing the association between depressive symptom severity and marital status, 25.7% (n=18) of those in a relationship and 17.6% (n=6) of those not in a relationship had borderline depressive symptoms. There was no statistically significant association between the severity of depressive symptoms and the marital status of caregivers working in COVID wards (p=0.504). Analysis of the association between life satisfaction and marital status showed that 19.4% (n=14) who were in a relationship and 10.5% (n=4) not in a relationship perceived a high level of life satisfaction. In contrast, 63.9% (n=46) of respondents in a relationship and 71.1% (n=27) not in a relationship were satisfied with their lives. No significant association was found between the level of life satisfaction and the marital status of the respondents, statistically (p=0.485) (Table 5).

Table 5. Assessment of the relationship between severity of anxiety and depression symptoms and life satisfaction and marital status among nurses working with severe acute respiratory syndrome coronavirus 2-infected patients (n=110)

Variable			Marital status		Chi2 test
			Being in a relationship	Not in a relationship	
HADS-M Anxiety	Normal	n	23	19	χ^2=5.995 df=2 p=0.050
		%	31.9	50	
	Borderline anxiety symptoms	n	25	14	
		%	34.7	36.8	
	Prominent anxiety symptoms	n	24	5	
		%	33.3	13.2	
Total		n	72	38	
		%	100	100	
HADS-M Depression	Normal	n	52	28	χ^2=0.446 df=1 p=0.504
		%	74.3	82.4	
	Borderline depression symptoms	n	18	6	
		%	25.7	17.6	
Total		n	70	34	
		%	100	100	
Satisfaction with life	Low	n	12	7	χ^2=1.446 df=2 p=0.485
		%	16.7	18.4	
	Average	n	46	27	
		%	63.9	71.1	
	High	n	14	4	
		%	19.4	10.5	
Total		n	72	38	
		%	100	100	

Legend: Chi^2/χ^2 – chi-squared; df – degrees of freedom; HADS-M – Hospital Anxiety and Depression Scale Modified Version; n – group quantity; p – statistical significance; % – percentage.

Table 6. Assessment of the relationship between severity of anxiety and depression symptoms and workplace among nurses working with severe acute respiratory syndrome coronavirus 2-infected patients (n=110)

Variable			Place of work				Chi^2 test
			Department of Internal Medicine	Department of Surgery	Department of Anesthesiology and Critical Care	Other	
HADS-M Anxiety	Normal	n	11	8	16	7	χ^2=24.987 df=6 p<0.001
		%	33.3	25	80	28	
	Borderline anxiety symptoms	n	9	18	2	10	
		%	27.3	56.3	10	40	
	Prominent anxiety symptoms	n	13	6	2	8	
		%	39.4	18.8	10	32	
Total		n	33	32	20	25	
		%	100	100	100	100	
HADS-M Depression	Normal	n	29	18	17	16	χ^2=9.941 df=3 p=0.019
		%	90.6	64.3	89.5	64.0	
	Borderline depression symptoms	n	3	10	2	9	
		%	9.4	35.7	10.5	36	
Total		n	32	28	19	25	
		%	100	100	100	100	

Legend: Chi^2/χ^2 – chi-squared; df – degrees of freedom; HADS-M – Hospital Anxiety and Depression Scale Modified Version; n – group quantity; p – statistical significance; % – percentage.

Relationship between severity of anxiety and depression symptoms and the workplace of nurses caring for severe acute respiratory syndrome coronavirus 2-infected patients

When analyzing the relationship between the severity of anxiety symptoms and the workplace, there were no anxiety symptoms observed in 33.3% (n=11) of respondents working in the Department of Internal Medicine, 25% (n=8) working in the Department of General Surgery, 80% (n=16) working in the Department of Anesthesiology and Critical Care, and 28% (n=7) working in other departments. Anxiety symptoms occurred significantly more often in those working in Anesthesiology and Critical Care units. A significant association existed between the severity of anxiety symptoms and the place of work, with anxiety symptoms occurring more often in those who worked in the Department of Internal Medicine, General Surgery, and other departments ($p<0.001$) (Table 6).

Analysis of the association between depressive symptom severity and work location demonstrated borderline depressive symptoms in 9.4% (n=3) of respondents who worked in the Department of Internal Medicine, 35.7% (n=10) who worked in the Department of General Surgery, 10.5% (n=2) who worked in the Department of Anesthesiology and Critical Care, and 36% (n=9) who worked in other departments. Borderline depressive symptoms occurred more frequently in respondents who worked in the Department of Surgery or other departments than in respondents who worked in the Department of Internal Medicine or the Department of Anesthesiology and Critical Care ($p=0.019$) (Table 6).

Relationship between life satisfaction and education of nurses working with severe acute respiratory syndrome coronavirus 2-infected patients

Of the respondents who graduated from high school or medical school, 60% (n=18) had an average level of life satisfaction, as did 70.8% (n=34) with a Bachelor of Nursing degree and 65.6% (n=21) with a Master of Nursing. In contrast, 20% (n=6) of respondents who graduated from high school or medical school, 14.6% (n=7) after a bachelor's degree, and 15.6% (n=5) after a master's degree, had a high level of satisfaction. There was no significant relationship between life satisfaction and respondents' education level ($p=0.903$) (Table 7).

Table 7. Assessment of the relationship between life satisfaction and education of nurses working with severe acute respiratory syndrome coronavirus 2-infected patients (n=110)

Variable			Education			Chi^2 test
			Secondary school or medical school	BA	MA	
Satisfaction with life	Low	n	6	7	6	$\chi^2=1.047$ df=4 p=0.903
		%	20	14.6	18.8	
	Average	n	18	34	21	
		%	60	70.8	65.6	
	High	n	6	7	5	
		%	20	14.6	15.6	
Total		n	30	48	32	
		%	100	100	100	

Legend: BA – bachelor's degree; Chi^2/χ^2 – chi-squared; df – degrees of freedom; MA – master's degree; n – group quantity; p – statistical significance; % – percentage.

Relationship between severity of anxiety and depression symptoms and life satisfaction of nurses working in coronavirus wards

Analysis of the relationship between the level of anxiety and life satisfaction showed significant anxiety symptoms in 36.8% (n=7) of nurses with low life satisfaction, 24.7% (n=18) with average life satisfaction, and 22.2% (n=4) with high life satisfaction. In addition, there were no abnormal anxiety symptoms in 10.5% (n=2) of participants with low life satisfaction, 42.5% (n=31) with average life satisfaction, and 50% (n=9) with high life satisfaction. There was no significant association between the severity of anxiety symptoms and participants' life satisfaction ($p=0.098$) (Table 8).

There was a relationship between the degree of depression and life satisfaction in 43.8% (n=7) of participants experiencing low life satisfaction, 22.9% (n=16) with average satisfaction, and 5.6% (n=1) with high satisfaction. Respondents experiencing low

Table 8. Assessment of the relationship between anxiety and depression levels and life satisfaction among nurses working with severe acute respiratory syndrome coronavirus 2-infected patients (n=110)

Variable			Satisfaction with life			Chi² test
			Low	Average	High	
HADS-M Anxiety	Normal	n	2	31	9	χ^2=7.821 df=4 p=0.098
		%	10.5	42.5	50	
	Borderline anxiety symptoms	n	10	24	5	
		%	52.6	32.9	27.8	
	Prominent anxiety symptoms	n	7	18	4	
		%	36.8	24.7	22.2	
Total		n	19	73	18	
		%	100	100	100	
HADS-M Depression	Normal	n	9	54	17	χ^2=6.967 df=2 p=0.031
		%	56.3	77.1	94.4	
	Borderline depression symptoms	n	7	16	1	
		%	43.8	22.9	5.6	
Total		n	16	70	18	
		%	100	100	100	

Legend: Chi²/χ^2 – chi-squared; df – degrees of freedom; HADS-M – Hospital Anxiety and Depression Scale Modified Version; n – group quantity; p – statistical significance; % – percentage.

life satisfaction were significantly more likely to have borderline depressive symptoms (p=0.031) (Table 8).

Discussion

The COVID-19 pandemic significantly impacted healthcare systems and increased the risk of mental health problems among healthcare workers. In particular, nurses were exposed to many psychosocial stressors and struggled with high workloads, inadequate resources, and uncertainty in the face of an unknown illness. Nonetheless, life satisfaction may protect nurses from the effects of chronic stress. The current study analyzed selected variables that may have influenced the severity of psychological problems and life satisfaction of nurses working directly with COVID-19 patients and assessed the relationship between life satisfaction and levels of anxiety, depression, and aggression. Working as a nurse was a sociodemographic factor associated with increased anxiety and depression. In addition, depressive disorders were associated with low life satisfaction.

Approximately one-quarter of nurses exhibited marked anxiety symptoms (26.3%, n=29), whereas 35.5% (n=39) had borderline anxiety. In addition, 5.5% (n=6) of the participants had depressive disorders, and 21.8% (n=24) had borderline depressive states. None of the study participants showed symptoms of aggression. A study of nurses and physicians from Wuhan in China confirmed that nurses working directly with COVID-19 patients were generally more prone to depression, anxiety, and stress than nurses who did not work under these specific conditions [17]. These results are also consistent with the findings of other authors [18,19]. Weilenmann et al. [20] found that nurses who dealt directly with COVID-19 patients reported more symptoms of anxiety, depression, and burnout than colleagues who did not. Similarly, Sarboozi et al. [21] found significantly higher burnout in nurses working on the frontline than in their colleagues working on regular wards. However, in some cases, nurses working on the frontline may have lower levels of burnout than nurses working in regular wards [22].

In the present study, age did not affect the level of anxiety (p=0.153) or depression (p=0.867) in nurses. Pronounced anxiety symptoms were observed in 18.2% (n=4) of subjects aged 20 to 30 years, 28.6% (n=10) aged 31 to 40 years, 27.3% (n=6) aged 41 to 50 years, and 29% (n=9) aged 50 years and older. Borderline depressive symptoms occurred in 28.6% (n=6) of 20 to 30-year-olds, 20.6% (n=7) of 31 to 40-year-olds, 19% (n=4) of 41 to 50-year-olds, and 25% (n=7) of nurses aged over 50 years. These results confirm the findings of other authors [23], who also found no significant effect of age on anxiety or depression. Nurses of all ages had anxiety but the reasons differed between groups. Indeed, younger workers were anxious about their families, while older people worried about the lack of adequate personal protective equipment and medical personnel, which translated into longer working hours [23].

A study among nurses and midwives working in different environments in Turkey, including private healthcare (PHC) and intensive care, where they had contact with infected patients, showed that the place of work did not affect the severity of anxiety or

depression symptoms. In addition, personnel who had first and direct contact with an infected patient had less fear of infection and displayed no symptoms of depression [7]. These findings corroborate a study on the long-term psychological and occupational effects of hospital healthcare during the SARS epidemic, which found no negative psychological effects of exposure to high-intensity, high-risk workplaces and direct contact with infected patients [24]. However, the current study showed that the workplace had a significant effect on the severity of anxiety ($p<0.001$) and depression symptoms ($p=0.019$). Anxiety symptoms were significantly more frequent in individuals who worked in the Department of Internal Medicine, General Surgery, and other departments. Meanwhile, borderline depressive symptoms were observed more frequently in respondents who worked in the Department of General Surgery and other departments than in respondents who worked in the Department of Internal Medicine and the Department of Anesthesiology and Critical Care. These results suggest that those working in higher-risk environments require special attention and should be the target group for psychological support programs.

There are no comparable studies in the literature assessing the association between marital status and levels of anxiety and depression in nurses working with SARS-CoV-2-infected patients. In this study, marital status had no significant effect on the severity of anxiety ($p=0.05$) or depression ($p=0.504$) in the participants.

Excessive negative emotions may lead to lower life satisfaction, as was demonstrated in a study by Świątek et al. on occupational burnout and life satisfaction in nurses. However, the authors did not investigate the relationship between age, education, marital status, and life satisfaction [1]. Nonetheless, other authors found that age, gender, and marital status were not significantly associated with life satisfaction [25], which was confirmed by the current research.

Nurses working with COVID-19-infected patients had an average level of life satisfaction ($p=0.001$). In addition, there was no significant relationship between the severity of anxiety symptoms and respondents' life satisfaction ($p=0.098$). However, respondents with low life satisfaction were significantly more likely to have borderline depressive symptoms ($p=0.031$).

In conclusion, the described characteristics provide a basis for more in-depth research on the topics and indicate that nurses working with SARS-CoV-2 -infected patients should receive psychological support. Furthermore, additional research is needed to distinguish between psychological symptoms during and after an infectious disease outbreak.

Limitations and future directions

Limitations of this study include the relatively small sample size and the fact that it involved only two medical institutions, which may limit the generalizability of the results. In the future, a multicenter study will aim to distinguish psychological symptoms during a pandemic from those after an outbreak.

Conclusions

The research presented in this study suggests that nursing staff working in COVID wards were more likely to exhibit anxiety symptoms than depression, and their life satisfaction was broadly average. There was no association between levels of anxiety and depression and age or marital status among nurses working with SARS-CoV-2-infected patients. In the study group, anxiety and depression were associated with work location. Indeed, anxiety symptoms were significantly more common among those who worked in internal medicine, general surgery, and other departments. Meanwhile, borderline depressive symptoms were significantly more common among respondents who worked in the Department of Surgery or other departments than respondents who worked in the Department of Internal Medicine and the Anesthesiology and Critical Care Unit. There was no association between life satisfaction and age, education, or marital status. However, nurses with low life satisfaction were significantly more likely to have borderline depressive symptoms.

References

1. Świątek A, Milecka D, Uchmanowicz I. Wypalenie zawodowe oraz satysfakcja z życia wśród pielęgniarek anestezjologicznych i intensywnej opieki. Współcz Pielęg Ochr Zdr 2017; 6(4): 121–128. (In Polish).
2. Skorupska-Król A, Szabla A, Bodys-Cupak I. Opinie pielęgniarek na temat czynników stresogennych związanych z ich środowiskiem pracy. Pielęg XXI w 2014;1(46): 23–2. (In Polish).
3. Kupcewicz E. Jakość życia pielęgniarek a strategie radzenia sobie ze stresem doświadczanym w środowisku pracy. Med Og Nauk Zdr 2017;23(1):62–67. (In Polish).
4. Szlenk-Czyczerska E, Ławnik A, Szepeluk A. Nurses' strategies for dealing with stress during the COVID-19 pandemic. Med Sci Pulse 2021; 15 (4):27–34.
5. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence of depression, anxiety, and in-

somnia among healthcare workers during the COVID-19 pandemic: a systematic review and meta-analysis. Brain Behav Immun 2020; 88: 901–907.

6. Dincer B, Inangil D. The effect of Emotional Freedom Techniques on nurses' stress, anxiety, and burnout levels during the COVID-19 pandemic: a randomized controlled trial. Explore (NY) 2020; 17(2): 109–114.
7. Yörük S, Güler D. The relationship between psychological resilience, burnout, stress, and sociodemographic factors with depression in nurses and midwives during the COVID-19 pandemic: a cross-sectional study in Turkey. Perspect Psychiatr Care 202; 57(1):390–398.
8. Stelnicki AM, Carleton RN, Reichert C. Nurses' mental health and well-being: COVID-19 impacts. Can J Nurs Res 2020; 52(3):237–239.
9. Al Maqbali M, Al Sinani M, Al-Lenjawi B. Prevalence of stress, depression, anxiety and sleep disturbance among nurses during the COVID-19 pandemic: a systematic review and meta-analysis. J Psychosom Res 2021; 141: 110343.
10. Salari N, Khazaie H, Hosseinian-Far A, Khaledi-Paveh B, Kazeminia M, Mohammadi M, et al. The prevalence of stress, anxiety and depression within front-line healthcare workers caring for COVID-19 patients: a systematic review and meta-regression. Hum Resour Health 2020; 18(1): 100.
11. Li Y, Scherer N, Felix L, Kuper H. Prevalence of depression, anxiety and post-traumatic stress disorder in health care workers during the COVID-19 pandemic: a systematic review and meta-analysis. PLoS One 2021; 16(3): e0246454.
12. Kliszcz J, Nowicka-Sauer K, Trzeciak B, Sadowska A. Poziom lęku, depresji i agresji u pielęgniarek, a ich satysfakcja z życia i z pracy zawodowej. Medycyna Pracy 2004; 55(6): 461–468. (In Polish).
13. Qu H-Y, Wang C-M. Study of the relationships between nurses' job burnout and subjective well-being. Chin Nurs Res 2015;2(2–3):61–6.
14. Kupcewicz E, Szczypiński W, Kędzia A. Satysfakcja z życia w kontekście życia zawodowego pielęgniarek. Piel Zdr Publ 2018; 8(1): 27–32. (In Polish).
15. Kozieł P, Lomper K, Uchmanowicz B, Polański J. Związek akceptacji choroby oraz lęku i depresji z oceną jakości życia pacjentek z chorobą nowotworową gruczołu piersiowego. Medycyna Paliatywna w Praktyce 2016; 10(1): 28–36. (In Polish).
16. Juczyński Z. Narzędzia pomiaru w promocji i psychologii zdrowia. Warszawa: Pracownia Testów Psychologicznych Polskiego Towarzystwa Psychologicznego; 2012: 128–135. (In Polish).
17. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open 2020; 3(3): 1–12.
18. Hu D, Kong Y, Li W, Han Q, Zhang X, Zhu LX, et al. Frontline nurses' burnout, anxiety, depression, and fear statuses and their associated factors during the COVID-19 outbreak in Wuhan, China: a large-scale cross-sectional study. E Clin Med 2020; 24: 100424.
19. Weilenmann S, Ernst J, Petry H, Pfaltz MC, Sazpinar O, Gehrke S, et al. Health care worker´s mental health during the first weeks of the sars-CoV-2 pandemic in Switzerland: a cross-sectional study. Front Psychiatry 2021; 12: 594340.
20. Sarboozi Hoseinabadi T, Kakhki S, Teimori G, Nayyeri S. Burnout and its influencing factors between frontline nurses and nurses from other wards during the outbreak of coronavirus disease- COVID 19 in Iran. Invest Educ Enferm 2020; 38(2): e3.
21. Wu Y, Wang J, Luo C, Hu S, Lin X, Anderson A, et al. A comparison of burnout frequency among oncology physicians and nurses working on the frontline and usual wards during the COVID-19 epidemic in Wuan, China. J Pain Symptom Manage 2020; 60(1): e60–5.
22. De Kock JH, Latham HA, Leslie SJ, Grindle M, Munoz SA, Ellis L, et al. A rapid review of the impact of COVID-19 on the mental health of healthcare workers: implications for supporting psychological well-being. BMC Public Health 2021;21:104.
23. Maunder RG, Lancee WJ, Balderson KE, Bennett JP, Borgundvaag B, Evans S, et al. Long-term psychological and occupational effects of providing hospital healthcare during SARS outbreak. Emerg Infect Dis 2006; 12(12): 1924–1932.
24. Yazdanshenas Ghazwin M, Kavian M, Ahmadloo M, Jarchi A, Javadi SG, et al. The association between life satisfaction and the extent of depression, anxiety and stress among iranian nurses: a multicentre survey. Iran J Psychiatry 2016; 11(2): 120–7.

Word count: 4864 • Tables: 8 • Figures: 0 • References: 24

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Szlenk-Czyczerska E, Włodarczyk M.
Evaluation of anxiety, depression, aggression, and life satisfaction of nurses working with severe acute respiratory syndrome coronavirus 2-infected patients.
Med Sci Pulse 2023;17(1):13–23. DOI: 10.5604/01.3001.0016.2348

Corresponding author:
Elżbieta Szlenk-Czyczerska
Email: ela6035@onet.pl
University of Opole, Poland

Other authors/contact:
Marta Włodarczyk
Email: wlodarczyk.marta98@onet.pl

Received: 13 November 2022
Reviewed: 24 January 2023
Accepted: 30 January 2023

e-ISSN 2544-1620

Medical Science Pulse 2023 (17) 1

Original papers

Published online: 27 February 2023

DOI: 10.5604/01.3001.0016.2849

PARKINSON'S DISEASE GENE THERAPY: A COMPARATIVE EFFECTIVENESS REVIEW OF COMPLETED CLINICAL TRIALS IN TERMS OF THEIR POSSIBLE IMPLEMENTATION IN TREATMENT

Marta Kozłowska[1 A-F]
• ORCID: 0000-0002-8870-4277

Szymon Kotarba[1 A-F]
• ORCID: 0000-0003-1271-9066

Jakub Tambor[1 B-F]
• ORCID: 0000-0001-9898-0526

Mateusz Winiarski[1 B-F]
• ORCID: 0000-0001-8386-5760

Hanna Moczulska[2 E]
• ORCID: 0000-0002-1815-3326

Michał Pietrusiński[2 E]
• ORCID: 0000-0002-9419-6221

Maciej Borowiec[2 E]
• ORCID: 0000-0003-2812-5676

[1] Student of the Medical Faculty, Medical University of Lodz, Poland

[2] Department of Clinical Genetics, Medical University of Lodz, Poland

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Parkinson's disease (PD) is a neurodegenerative disease in which dopaminergic neurons are damaged, and Lewy bodies accumulate in the brain, leading to both motor and non-motor symptoms. Currently, no treatment is available to slow down or reverse disease progression. The need to find new solutions has prompted research interest in gene therapy.

Aim of the study: The purpose of this review is to analyze a selection of completed clinical trials on gene therapy in PD and their possible implementation in treatment.

Material and methods: Clinical trials were selected from the ClinicalTrials.gov database using the following search criteria: Parkinson's disease, gene therapy, and completed status. Trials that were ongoing, terminated, preclinical, or with different research subjects were excluded. PubMed and Google Scholar databases were also searched for neuropathology, symptoms, and treatment recommendations for PD. The results of reviewed clinical trials have been checked in terms of the efficacy and safety of the investigated therapies in the treatment of PD.

Results: We analyzed 7 completed clinical trials, namely VY-AADC01 (NCT01973543), AAV-GAD (NCT00195143), ProSavin (NCT00627588), AAV2-GDNF (NCT01621581), CERE-120 (NCT00252850), VY-AADC01 (NCT03065192), and CERE-120 (NCT00985517) with a total of 152 patients. Five of the studies had published results and four of these five had satisfactory results. VY-AADC01, AAV-GAD, and CERE-120 were found to be safe and potentially effective in the treatment of PD, while ProSavin demonstrated insufficient effectiveness.

Conclusions: There is limited available data regarding completed clinical trials for PD gene therapy, with a small number of patients, making it difficult to give a final statement on the possibility of using gene therapy to treat PD. However, the clinical trials reviewed herein show promising results with the potential to revolutionize the treatment of PD.

KEYWORDS: Parkinson's Disease, gene therapy, clinical trials, AAV vector

Background

Parkinson's disease (PD) is the second most common neurodegenerative disease with motor and non-motor symptoms [1]. In the course of this disease, the dopaminergic neurons of the substantia nigra are damaged, and Lewy bodies composed of incorrectly folded proteins accumulate in the brain [2]. The cause of idiopathic PD is unknown but is associated with risk factors, including aging, family history, pesticide exposure, and environmental chemicals [3]. Smokers and coffee and tea drinkers are among the lowest-risk groups. The disease most often affects the elderly, and men are at a 1.5 times greater risk of developing PD than women [4]. Diagnosis is based on clinical symptoms, family history, and neurological examination, while imaging methods such as MRI can be used for the differential diagnosis to rule out other neurodegenerative diseases [5]. The most dominant symptoms of PD are termed the "cardinal signs" and include tremors, slowness of movement (bradykinesia), rigidity, and postural instability. Some additional motor symptoms include hypomimia, emotionless face, soft, monotonous speech, 'shuffling' gait, and micrography. Non-motor symptoms of the disease, including depression, dementia, anxiety, psychotic, sexual and sleep disorders, pain, constipation, hyperhidrosis, orthostatic hypotension, seborrheic dermatitis, or nocturia lead to a substantial deterioration of life [3].

The onset of symptoms is associated with the loss of 60-70% of substantia nigra pars compacta [6]. It should be noted that PD is a progressive disease, meaning symptoms exacerbate over time [7]. The current gold-standard PD treatment is Levodopa (L-DOPA), a dopamine precursor that alleviates symptoms, particularly bradykinesia and stiffness [8]. As the disease progresses, the duration of L-DOPA action is reduced and the dose must be increased. Additionally, dopamine agonists, MAO-B inhibitors, or catechol-O-methyl transferase (COMT) inhibitors are used. When the disease becomes advanced, motor fluctuations start to occur despite pharmacological treatment [3, 5]. When drug therapies fail, deep brain stimulation (DBS) may be considered [9]. DBS is the surgical placement of electrodes into part of the brain, most commonly the low thalamic nucleus [10]. The effects of DBS therapy include improving Unified Parkinson Disease Rating Scale (UPDRS) II (activities of daily living) and UPDRS III (motor symptoms) scores by approximately 50-60%, reducing the dose of dopaminergic drugs, and alleviating dyskinesias. An important limitation of this method is the restrictive list of exclusion criteria [11]. According to the National Institute for Health and Care Excellence (NICE) recommendation, patients with PD should follow a diet consisting mainly of a protein supply, but it is crucial to consume most of the protein daily intake in the evening. That is because proteins decrease the absorption of levodopa [5,12]. Furthermore, patients experiencing balance or motor problems may be referred for physical therapy [5].

There is no current cure for PD, and no current treatment results in the slowing down or reversal of disease progression [7]. This need to find new solutions has recently prompted scientists to investigate the potential of gene therapy. Gene therapy is a form of therapy that manages disease by introducing a therapeutic gene using a vector, such as a non-pathogenic virus (for example, Adeno-associated virus AAV or lentivirus) [13]. The effects of gene therapy can be achieved in many ways. Examples include the replacement of a defective gene with its correct copy, the inactivation of a disease-causing gene, or the introduction of an additional gene with therapeutic properties into the cell [14]. Gene therapy has already been approved by the European Union for the treatment of conditions such as adenosine deaminase deficiency, severe combined immunodeficiency (SCID X1), and adrenoleukodystrophy [15]. There are also studies on the use of gene therapy in the treatment of neurodegenerative diseases such as PD (a list of the studies can be found at ClinicalTrials.gov).

Aim of the study

The purpose of this review was to analyze a selection of completed clinical trials on gene therapy in PD in terms of their possible implementation in patient treatments.

Material and methods

The clinical trials for this study were selected using the ClinicalTrials.gov database. The search

terms included "Parkinson's disease", "gene therapy", and completed status. Trials were excluded if they were ongoing, terminated, or preclinical trials. The PubMed, Google Scholar, ClinicalTrials.gov, FDA, NHS, and National Institute for Health and Excellence databases were searched (in July 2022). Only articles written in English or Polish were screened.

PubMed and Google Scholar databases were used to collect articles on neuropathology, symptoms, and treatment recommendations for PD. Terms such as "gene therapy", "Parkinson's disease", and "AAV vector" were used for searches to conduct the review. The filters included the "completed" status of trials, as well as the newest publications regarding the topic. Inclusion criteria for searched data were PD, gene therapy, clinical trial-focused studies, and the type of article (original paper, review, or meta-analysis). Case reports, as well as registers submitted before 2008, with only an abstract available or not related to PD, were excluded. The NICE database was searched for recommendations on PD treatment. Furthermore, the Food and Drug Administration database was searched for general information about gene therapy.

The collected data were divided into groups, namely PD symptoms, neuropathology of PD, gene therapy, and PD treatment. Titles and abstracts of articles were read, and if they matched the inclusion criteria, the authors screened full-text articles and decided whether they were eligible for the review. Four authors worked independently on searching the articles, then the registers were double-checked by two of them. Each clinical trial was examined in terms of the number of patients, masking used, sponsors, and investigators to assess the certainty of an outcome. No automatization tools were used in the process of collecting data. Throughout this review, we highlight relevant data in several tables to present the risk of bias and clinical trial statistics.

Study risk of bias assessment

Table 1. The risk of bias, based on the data contained in Table 2

Therapy	Selection bias	Performance bias	Detection bias
VY-AADC01 (1)	High risk	High risk	Low risk
AAV-GAD	High risk	High risk	High risk
ProSavin	Low risk	High risk	High risk
AAV2-GDNF	High risk	High risk	High risk
CERE-120 (1) (AAV2-NTN)	High risk	High risk	High risk
VY-AADC01 (2)	N/A	High risk	High risk
CERE-120 (2) (AAV2-NTN)	Low risk	Very low risk	Very low risk

RESULTS

At first, 33 clinical trials were found at ClinicalTrials.gov, and the ongoing, terminated, or preclinical trials (23 studies) were excluded. Three of the remaining studies were excluded because they did not coincide with the research topic. Search results that were consistent with the subject of this review were selected (7 studies). The results of the reviewed clinical trials have been checked in terms of the efficacy and safety of the investigated therapies in the treatment of PD. The search process used for the literature review is depicted in Fig. 1.

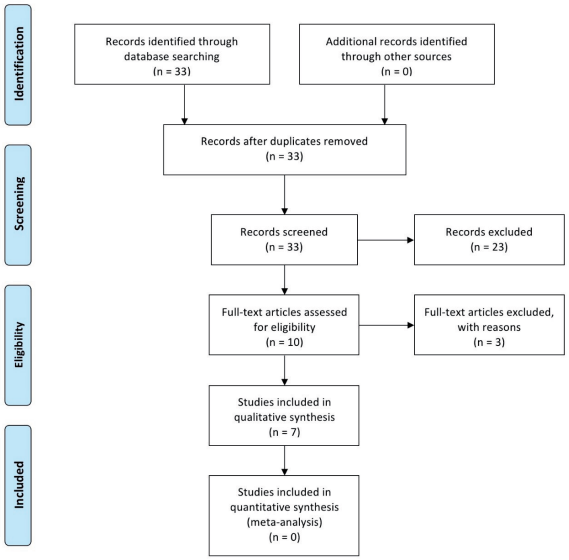

Figure 1. PRISMA 2009 Flow Diagram [16] (for more information, visit www.prisma-statement.org)

AADC (VY-AADC01)

Aromatic L-Amino Acid Decarboxylase (AADC) is the enzyme responsible for the synthesis of dopamine from levodopa. As PD progresses, a decreased expression of AADC is observed, which is associated with the loss of the dopaminergic nigrostriatal pathway. This process causes an exacerbation of disease symptoms and a decrease in the effectiveness of Levodopa treatment (patients must take increasingly larger doses) [13]. AADC gene therapy has successfully passed Phase 1 (conducted between 2013-2020) of clinical trials in terms of safety and effectiveness in the treatment of PD [17].

In this trial, the study medication VY-AADC01 was administered to 15 patients in three doses directly into the striatum during real-time MRI-guided neurosurgery. The vector was the non-pathogenic adeno-associated virus 2 (AAV2) viral vector of the Parvovirus family, which causes a mild immune response. The study was carried out among patients aged 40-70

years suffering from intermediate idiopathic Parkinson's disease for at least 5 years. These patients remained sensitive to dopaminergic treatment, and the demand for medication decreased by an average of 21-30% in the second-highest dose group at 36 months**.** Standard measures of motor function, global impressions of improvement, and quality of life were stable or improved compared with baseline at 12, 24, and 36 months following VY-AADC01 administration. No serious side effects were noted, and any minor effects disappeared over time.

Treatment resulted in increased activity of the AADC enzyme in the striatum. The results of the study in a specific group of patients indicate the safety and tolerance of VY-AADC01 and the neurosurgical procedure. While AADC gene therapy offers new possibilities in the treatment of PD, further research should be carried out to obtain the optimal treatment dose [18].

Another study investigated the safety of complete AADC gene therapy with VY-AADC-01. Sixteen people with developed PD, who were not administered L-Dopa treatment, underwent surgery involving the MRI-guided introduction of the drug with a viral vector into the striatum of both hemispheres. The procedure demanded the use of MRI during the procedure to control brain function. Participants were instructed to record and monitor their health status, and further investigations were performed consisting of laboratory tests, cognitive functions, and assessment of the patient's condition by specialists. This study has been completed, but no unequivocal safety results have been published yet [19].

AAV-GAD

One of the causes of symptoms in PD is abnormal neurotransmission within the basal ganglia pathways responsible for deliberate movement. The pathology within these brain regions is triggered by the lack of inhibition caused by the decreased secretion of the neurotransmitter gamma-aminobutyric acid (GABA). One of the structures affected by this disinhibition is the Subthalamic nucleus (STN). GABA-induced over-excitement in the STN disrupts the transmission pathways associated with the Globus pallidus (GP) and substantia nigra pars reticulata (SNpr). Due to STN pathology, those regions (GP and SNr) also have reduced GABA concentrations. AAV-GAD Gene therapy uses an AAV viral vector associated with the glutamate decarboxylase (GAD) gene and aims to increase the synthesis of inhibitory neurotransmitters in this area of the brain to restore the proper function of neurons. The gene used in therapy is *GAD*, which enhances GABA synthesis. This results in an increase of GABA to normal levels.

In testing this therapy, 45 patients aged 30-75 years (suffering from progressive PD) were treated with L-DOPA. Twenty-three of them underwent sham surgery, and twenty-two received an intracerebral injection of AAV2-GAD, and patients were reviewed 6 months later. There was a marked improvement in the UPDRS in the group that received AAV2-GAD compared to the placebo group. However, after therapy, several postoperative complications and other symptoms occurred, including a higher incidence of dizziness and headache in AAV2-GAD patients [20]. No other side effects were noticed. Furthermore, the safety study of AAV2-GAD therapy was positive [20], being safe and well-tolerated by patients with PD [20, 21]. This novel therapy holds promise for a new approach to the treatment of PD, and it is possible that, in combination with existing treatments, it would make it easier for people with PD to cope with everyday difficulties. However, this requires more research to test the long-term effects of such therapy.

ProSavin

One of the treatments tested for PD is gene therapy using ProSavin. This therapy consists of a lentiviral carrier containing three genes, coding for L-aromatic amino acid decarboxylase, tyrosine hydroxylase, and GTP cyclohydrolase I. The bilateral injection of ProSavin is implemented into the striatum of PD patients to stimulate dopamine secretion [22, 23]. Phase 1/2 clinical trials took place in both France and the UK to ensure the safety and effectiveness of the therapy, and to determine the dosage of ProSavin. These studies involved 15 patients who were divided into 3 groups. Each group was injected with different dosages of ProSavin into the putamen (3 patients received a low drug concentration, 6 patients received a moderate dose, and 6 received a high dose). Then researchers monitored the number and severity of side effects and assessed the changes in the patient's motor skills using the UPDRS.

Patients who received Prosavin had to meet the following criteria, namely being between 48-to-65 years of age, having a disease duration of more than 5 years with motor disorders, and having at least 50% response to oral dopamine replacement therapy. The subjects did not take dopamine analogs during the study. After the first 12 months of the trial, 54 side effects were found to be associated with taking ProSavin (51 of them were mild and 3 were moderate). The most common complications were dyskinesia (affected 11 patients) and on-off phenomenon (9 patients). There were no serious adverse effects associated with the therapy, and all patients had an increase in mean scores on the UPDRS sheet after 6 and 12 months.

ProSavin is safe for use in patients with advanced PD. While the drug improved motor function in all the participants, this did not reach significance compared to baseline, according to the researchers. It is promising that Oxford Biomedica has developed a new drug based on ProSavin, namely AXO-Lenti-PD, showing even better improvement of motor function in studies conducted with macaque monkeys [24,25].

AAV2-GDNF

Glial cell line-derived neurotrophic factor (GDNF) has protective properties for dopaminergic neurons, the destruction of which is the likely cause of PD. The aim of the clinical trial, conducted by a team of scientists from the National Institute of Neurological Disorders and Stroke, was to assess the safety and effectiveness of gene therapy involving the insertion of a gene encoding GDNF into the putamen. The study involved 24 patients who received treatment by a neurosurgical operation to introduce an AAV containing the GDNF gene (AAV2-GDNF). The patients participating in the study were divided into 4 groups of 6 people, and each group was administered a different dose of AAV2-GDNF.

Adults with PD, who showed a poor response to conventional treatment, were enrolled in this study. Other inclusion criteria were idiopathic PD, or the presence of at least 3 of the following clinical symptoms: resting tremor, cogwheel rigidity, bradykinesia, or postural reflex impairment.

For the first 5 years, patients were regularly monitored for side effects of the therapy using methods such as lumbar puncture and neurological examination. Then, their response to treatment was examined through clinical and laboratory tests, as well as with the use of MRI. Unfortunately, the results of the study have not been made available as of today, so it is not yet possible to determine the safety and efficacy of therapy with the use of AAV2-GDNF [26, 27].

CERE-120

CERE-120 is another proposal for PD gene therapy. It is again based on an AAV viral vector encoding the neurturin gene (NTN). NTN is a neurotropic factor that takes part in regulating survival and the function of neurons. The premise of this therapy is that gene transfer of NTN may improve the function of neurons and protect against further neurodegeneration [28]. A completed open-label Phase One clinical trial of CERE-120 confirms it is safe and efficacious for use in humans.

Twelve patients aged 35-75 years with a diagnosis of bilateral idiopathic PD for at least 5 years with motor fluctuations (despite adequate oral anti-parkinsonian therapy) received bilateral stereotactic injections using computer-assisted trajectory planning. One dose of CERE-120 was implemented into the putaminal region of the brain. The study was conducted in two groups, with half of the subjects receiving a low dose, and the other half a high dose. Patients were followed up for the next 12 months, and there were no serious adverse events and no off-medication dyskinesia associated with the therapy. Off-medication motor sub-score of the UPDRS was improved in all patients, and the period without troublesome dyskinesia was significantly improved. CERE-120 proved to be safe and effective, although the presented study should be considered preliminary due to the small number of patients, short monitoring time (1 year), and open-label nature [29, 30].

Another study on the safety of CERE-120 therapy was carried out on a group of 57 patients with PD. In addition to determining the drug's safety, the study also aimed to monitor the anticipated therapeutic effects. In the first phase of the study, 3 patients received a lower dose, and 3 received a higher dose of the non-pathogenic AAV viral vector containing the gene encoding the protein from the group of GDNF trophic factors, namely neurturin. The drug was directly inserted into dopaminergic neurons in the putamen and the substantia nigra. In the second phase, 24 participants received the actual dose of CERE-120, while the other 27 underwent sham surgery without the injection of medication. Participants were monitored for 5 years after surgery to determine the impact of CERE-120 on the course of PD. This study has been completed and the results were published. The most prominent adverse effects were incision site pain, dyskinesias, and headache, all of which were associated with the surgery rather than the AAV2-NRTN treatment. No subjects from phase 2 experienced any clinically significant adverse events. Furthermore, MRI scans performed after the procedure showed no abnormalities. This research shows that CERE-120 is a promising safe and efficacious PD therapy [31].

Discussion

In this review, we analyzed 7 completed clinical trials, 5 of which had published results, and 4 of these 5 had satisfactory results [17, 19, 21, 25, 27, 30, 31]. The AADC gene therapy described above was considered safe and potentially effective. It can be used as an adjunct to Levodopa therapy as patients who underwent AADC therapy have a reduced need for pharmacological interventions for PD [17]. Increased activity of the AADC enzyme has been noticed in the putamen in the medium of spiny neurons, which do not degenerate in PD. It enables the creation of an

alternative pathway for the conversion of levodopa to dopamine. However, the therapy does not inhibit the degeneration of dopaminergic neurons, so it does not affect the progression of the disease, although the quality of life and motor functions may be improved by the therapy [18]. To accurately assess the efficacy and dose required, further studies must be carried out on a larger group of patients, using blinding and randomization. CERE-120 has been shown to be safe and effective. Patients improved their UPDRS scores, and time without troublesome dyskinesias was increased [30,31]. In addition, it has been shown in animal studies that the transfer of the NTN-encoding gene can occur selectively to neurons of the nigrostriatal pathway, and the effects of such therapy may persist for at least one year. Although many of the effects of CERE-120 therapy had significant clinical importance, some of them (objective assessment of timed walking and hand dexterity) turned out to be statistically insignificant [29]. ProSavin was also shown to be safe and effective, but the optimal level of dopamine replacement was not achieved as patients required oral L-Dopa administration to maximize the therapeutic effect. That is why research on OXB-2 (AXO-Lenti-PD) is being conducted, which, in preclinical studies, has shown significantly greater effectiveness than ProSavin [32]. The limitation of gene therapies analyzed in this article is the inclusion criterion for study patients, which was a moderately advanced or advanced idiopathic form of PD. No data showed the safety and efficacy of the tested gene therapies in patients suffering from other variants of PD. Furthermore, the above gene therapies require neurosurgical intervention, and patients must be properly qualified for surgery, meaning not all patients can participate due to co-morbidities or advanced age. Furthermore, the cost of gene therapy can be very high; a single administration of abopervovec used in spinal muscular atrophy costs USD$2.125 million. Another (non-gene) therapy involving the administration of Factor XIII in hemophilia A costs between USD$15-18 million. However, the administration of abopervovec is once-in-a-lifetime, while Factor XIII must be administered until the end of life. New gene therapies are overpriced due to the "theory of second best" effect (which concerns the situation when one or more optimal conditions cannot be satisfied) [33]. The cost is also influenced by the rarity of the disease and the rate of therapeutic effectiveness [34]. Hence, the cost of gene therapy varies in different countries from several thousand to several million USD [35]. The high cost may limit the group of therapy recipients to the richest patients. We failed to find a fixed gene therapy cost in the targeting of PD.

Table 2. The scientific value of the studies mentioned earlier in the article: VY-AADC01 (1), AAV-GAD, ProSavin, AAV2-GDNF, CERE-120 (1), VY-AADC01 (2), CERE-120 (2). The CERE-120 (2) is the most statistically powerful research [17, 19, 21, 25, 27, 30, 31]

Therapy	Allocation	Masking	Time period	Enrollment
VY-AADC01 (1)	Non-randomized	single	October 2013 – January 24, 2020	15
AAV-GAD	Non-randomized	None (open-label)	August 2003 – August 2005	12
ProSavin	Randomized	None (open-label)	January 2008 – August 2012	15
AAV2-GDNF	Non-randomized	None (open-label)	March 13, 2013 – February 4, 2022	25
CERE-120 (1) (AAV2-NTN)	Non-randomized	None (open-label)	June 2005 – March 2007	12
VY-AADC01 (2)	N/A	None (open-label)	May 11, 2017 – August 10, 2021	16
CERE-120 (2) (AAV2-NTN)	Randomized	Quadruple (participant, care provider, investigator, outcome assessor)	October 29, 2009 – November 16, 2017	57

Clinical trials examining gene therapy to treat PD are continuing, although ongoing research may reveal different approaches. Due to the possibilities offered by gene therapy, multiple investigations are also being conducted on other neurodegenerative diseases, such as Alzheimer's disease [36] or Batten's disease [37].

Limitations

An important limitation encountered in this review is the small number of completed clinical trials for PD gene therapy. The patient groups are small, and the choice of patients is not based on specific and constant criteria (different ages, different disease origins or types, different dominant symptoms, and different ancillary treatments). This makes it difficult to give a unanimous statement on the possibility of using gene therapy in the treatment of PD. Final judgment should be held until more research is completed.

Conclusions

The currently available PD treatments aim to relieve symptoms of the disease but do not prevent the loss of dopaminergic neurons. As of today, no therapy has yet been approved to inhibit disease progression,

but clinical trials on the treatment of PD with gene therapy show promising results, and further investigations should be held to determine what kind of patients would benefit. Because of the limited number of people examined and inconsistent factors, there were a lot of discrepancies, which must be taken into consideration when preparing for the next trials. Until then, we cannot draw a solid conclusion, but gene therapy has great potential to revolutionize the treatment of PD and other neurodegenerative disorders.

References

1. Sherer TB, Chowdhury S, Peabody K, Brooks DW. Overcoming obstacles in Parkinson's disease. Mov Disord 2012; 27:1606-1611.
2. MacPhee G, Stewart D. Parkinson's disease. Reviews in Clinical Gerontology 2001; 11: 33- 49.
3. Sławek J. Choroba Parkinsona: jak właściwie rozpoznawać, skutecznie i bezpiecznie leczyć? [Parkinson's disease – how to properly diagnose and effectively and safely treat?]. Forum Med Rodz 2014; 8: 281–329. (In Polish).
4. Kalia LV, Lang AE. Parkinson's disease. Lancet 2015; 386: 896–912.
5. National Institute for Health and Care and Excellence. Parkinson's disease in adults. NICE guideline [NG71] 19 July 2017 [online] [cited 28.07.2022]. Available from URL: https://www.nice.org.uk/guidance/ng71/chapter/recommendations.
6. Postuma RB, Gagnon JF, Montplaisir J. Clinical prediction of Parkinson's disease: planning for the age of neuroprotection. J Neurol Neurosurg Psychiatry 2010; 81: 1008-1013.
7. National Health Institute. Parkinson's disease [online] [cited 28.07.2022]. Available from URL: https://www.nhs.uk/conditions/parkinsons-disease.
8. Ovallath S, Sulthana B. Levodopa: history and therapeutic applications. Ann Indian Acad Neurol 2017; 20: 185-189.
9. Radhakrishnan DM, Goyal V. Parkinson's disease: a review. Neurol India 2018; 66: 26-35.
10. Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol 2016; 115: 19-38.
11. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. Lancet Neurol 2013; 12: 1025-1034.
12. Karbowniczek A, Sienkiewicz-Jarosz H, Czernuszenko A, Kłęk S, Sobów T, Sławek J. Leczenie żywieniowe w neurologii – stanowisko interdyscyplinarnej grupy ekspertów. Część 2. Rola żywienia w chorobie Parkinsona [Clinical nutrition in neurology-stance of interdisciplinary group of experts. Part 2. Role of nutrition in Parkinson's disease]. Pol Prz Neurol 2018; 14: 117–130. (In Polish).
13. Axelsen TM, Woldbye DPD. Gene therapy for Parkinson's disease, an update. J Parkinsons Dis 2018; 8: 195-215.
14. Food and drug administration, HHS. Long term follow-up after administration of human gene therapy products; guidance for industry. [online] [cited 28.07.2022]. Available from URL: https://www.federalregister.gov/documents/2020/01/30/2020-01710/longterm-follow-up-after-administration-of-human-gene-therapy-products-guidance-for-industry.
15. Wirth T, Parker N, Ylä-Herttuala S. History of gene therapy. Gene 2013; 10: 162-169.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med 6(7): e1000097.
17. Safety study of AADC gene therapy (VY-AADC01) for Parkinson's disease (AADC). NCT01973543. ClinicalTrials.gov. 2020, March 3 [online] [cited 28.07.2022]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT01973543?term=Gene+therapy&recrs=e&cond=Parkinson+Disease&draw=2&rank=1.
18. Christine CW, Richardson RM, Van Laar AD, Thompson ME, Fine EM, Khwaja OS, et al. Safety of AADC gene therapy for moderately advanced Parkinson disease: three-year outcomes from the PD-1101 trial. Neurology 2022; 98:40-50.
19. Safety and efficacy study of VY-AADC01 for advanced Parkinson's disease. NCT03065192. ClinicalTrials.gov. 2022, March 21 [online] [cited 28.07.2022]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT03065192?term=Gene+therapy&recrs=e&cond=Parkinson+Disease&draw=2&rank=6.
20. LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, Flaherty AW, Eskandar EN, et al. AAV2- GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomized trial. Lancet Neurol 2011; 10:309-319.
21. Safety study of subthalamic nucleus gene therapy for Parkinson's disease. NCT00195143. ClinicalTrials.gov. 2008, March 27 [online] [cited 28.07.2022] Available from URL: https://clinicaltrials.gov/ct2/show/study/NCT00195143?term=gene+therapy&recrs=e&cond=Parkinson+Disease&draw=2&rank=2.
22. Oxford Biomedica PLC. Positive results in Phase I/II trial. 2008 Nov 19 [online] [cited 28.07.2022]. Available from URL: https://www.oxb.com/investors/regulatory-news/positive-results-phase-iiitrial.
23. Jarraya B, Boulet S, Ralph GS, Jan C, Bonvento G, Azzouz M, et al. Dopamine gene therapy for Parkinson's disease in a nonhuman primate without associated dyskinesia. Sci Transl Med 2009; 1:2-4.
24. Badin RA, Binley K, Van Camp N, Jan C, Gourlay J, Robert C, Gipchtein P, et al. Gene therapy for Parkinson's disease: preclinical evaluation of optimally configured TH:CH1 fusion for maximal dopamine synthesis. Mol Ther Methods Clin Dev 2019; 14: 206-216.
25. Phase I/II study of the safety, efficacy and dose evaluation of ProSavin for the treatment of bilateral idiopathic Parkinson's disease. NCT00627588. ClinicalTrials.gov. 2013, May 13 [online] [cited 28.07.2022]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT00627588?term=Gene+therapy&recrs=e&cond=Parkinson+Disease&draw=1&rank=3.
26. McFarthing K, Prakash N, Simuni T. Clinical trial highlights: 1. gene therapy for Parkinson's, 2. phase 3 study in focus –

INTEC PHARMA'S accordion pill, 3. clinical trials resources. J Parkinsons Dis 2019; 9: 251- 264.

27. AAV2-GDNF for advanced Parkinson s disease. NCT01621581. ClinicalTrials.gov. 2022, July 25 [online] [cited 28.07.2022]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT01621581?term=Gene+therapy&recrs=e&cond=Parkinson+Disease&draw=2&rank=4.

28. Herzog CD, Dass B, Gasmi M, Bakay R, Stansell JE, Tuszynski M, et al. Transgene expression, bioactivity, and safety of CERE-120 (AAV2-neurturin) following delivery to the monkey striatum. Mol Ther 2008; 16: 1737-1744.

29. Marks WJ Jr, Ostrem JL, Verhagen L, Starr PA, Larson PS, Bakay RA, et al. Safety and tolerability of intraputaminal delivery of CERE-120 (adeno-associated virus serotype 2- neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial. Lancet Neurol 2008; 7: 400-408.

30. Safety of CERE-120 (AAV2-NTN) in subjects with idiopathic Parkinson's disease. NCT00252850. ClinicalTrials.gov. 2016, Sept 7 [online] [cited 28.07.2022]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT00252850?term=Gene+therapy&recrs=e&cond=Parkinson+Disease&draw=2&rank=5.

31. Safety and efficacy of CERE-120 in subjects with Parkinson's disease. NCT00985517. ClinicalTrials.gov. 2020, April 16 [online] [cited 28.07.2022]. Available from URL: https://clinicaltrials.gov/ct2/show/study/NCT00985517?term=Gene+therapy&recrs=e&cond=Parkinson+Disease&draw=2&rank=7.

32. Palfi S, Gurruchaga JM, Lepetit H, Howard K, Scott Ralph G, Mason S, et. al. Long-term follow-up of a phase I/II study of ProSavin, a lentiviral vector gene therapy for Parkinson's disease. Hum Gene Ther Clin Dev 2018; 29: 148-155.

33. Lipsey RG, Lancaster K. The general theory of second best. Review of Economic Studies 1956; 24: 11–32.

34. Garrison LP Jr, Jiao B, Dabbous O. Gene therapy may not be as expensive as people think: challenges in assessing the value of single and short-term therapies. J Manag Care Spec Pharm 2021; 27: 674-681.

35. Shukla V, Seoane-Vazquez E, Fawaz S, Brown L, Rodriguez-Monguio R. The landscape of cellular and gene therapy products: authorization, discontinuations, and cost. Hum Gene Ther Clin Dev 2019; 30: 102-113.

36. CERE-110 in subjects with mild to moderate Alzheimer's disease. NCT00087789. ClinicalTrials.gov. 2016 Oct 31 [online] [cited 28.07.2022]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT00087789).

37. Safety study of a gene transfer vector for children with late infantile neuronal ceroid lipofuscinosis. NCT00151216. ClinicalTrials.gov 2020 July 24. [online] [cited 28.07.2022]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT00151216.

Word count: 3711 • Tables: 2 • Figures: 1 • References: 37

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Kozłowska M, Kotarba S, Tambor J, Winiarski M, Moczulska H, Pietrusiński M, Borowiec M.
Parkinson's disease gene therapy: a comparative effectiveness review of completed clinical trials in terms of their possible implementation in treatment.
Med Sci Pulse 2023;17(1):24–31. DOI: 10.5604/01.3001.0016.2849

Corresponding author:
Marta Kozłowska
Email: Marta.kozlowska1@stud.umed.lodz.pl
Medical University of Lodz, Poland

Other authors/contact:
Szymon Kotarba
Email: Szymon.kotarba@stud.umed.lodz.pl

Jakub Tambor
Email: Jakub.tambor@stud.umed.lodz.pl

Mateusz Winiarski
Email:Mateusz.winiarski@stud.umed.lodz.pl

Hanna Moczulska
Email: Hanna.moczulska@umed.lodz.pl

Michał Pietrusiński
Email: Maichal.pietrusinski@umed.lodz.pl

Maciej Borowiec
Email:Maciej.borowiec@umed.lodz.pl

Received: 01 August 2022
Reviewed: 12 February 2023
Accepted: 27 February 2023

e-ISSN 2544-1620

Medical Science Pulse 2023 (17) 1

Original papers

Published online: 19 March 2023

DOI: 10.5604/01.3001.0016.3153

PATIENT RISK FACTORS AND NODULE CHARACTERISTICS FOR DIFFERENTIATING BENIGN FROM MALIGNANT PULMONARY NODULES

Hulya Dirol[1 A-F]
• ORCID: 0000-0002-7712-6467

Ayse Keven[2 A,B,D,E,G]
• ORCID: 0000-0002-1662-8586

Ege Alkan[3 A-C,F,G]
• ORCID: 0000-0002-7805-5808

[1] Chest Department, Akdeniz University Hospital, Antalya, Turkey

[2] Department of Radiology, Akdeniz University Hospital, Antalya, Turkey

[3] Anatomy Department, Akdeniz University Hospital, Antalya, Turkey

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: We have been encountering pulmonary nodules more frequently due to increased lung cancer screening programs and lung computed tomography imaging for other reasons. Although various guidelines have been developed regarding pulmonary nodules, uncertainty continues regarding the follow-up and management of pulmonary nodules.

Aim of the study: To define the patient risk factors and pulmonary nodule characteristics that differentiate malignant nodules from benign nodules.

Material and methods: Patients with pulmonary nodules detected between August 2014 and January 2019 in a university hospital were analyzed retrospectively. Data about patient risk factors (age, gender, smoking history, occupational and environmental risk factors, comorbidities, cancer history, and family history) and nodule characteristics (nodule diameter, nodule type, border properties, and nodule localization) were obtained. The features of malignant nodules and benign nodules were examined.

Results: There were 40 patients with pulmonary nodules whose final diagnosis could be classified as benign or malignant. The mean age was 63.28±12.06 years. Twenty-two (55%) patients were female. Eleven (27.5%) patients had never smoked. Nineteen (47.5%) patients were asymptomatic. Two of the nodules were malignant. There were no significant differences in mean age, gender, smoking history, comorbidities, occupational and environmental risk factors, familial risk factors, nodule type, nodule localization, nodule size, or nodule border properties between the benign and malignant nodules.

Conclusions: There is considerable overlap in nodule characteristics and patient risk factors between benign and malignant pulmonary nodules. Despite a comprehensive clinical and radiological evaluation, it is not easy to determine whether a nodule is benign or malignant.

KEYWORDS: pulmonary nodule, malignant, benign, chest computed tomography

Background

Pulmonary nodules are lesions smaller than 30 mm that are completely surrounded by lung parenchyma [1]. Many pulmonary nodules are detected incidentally in cancer screening studies or in chest computed tomography (CT) taken for another reason. Following the detection of the pulmonary nodule, the main problem arises in accurately assessing and managing the possibility of malignancy.

Accurate identification and characterization of malignant pulmonary nodules and the creation of

more precise algorithms for nodule management will increase the chance of cure in lung cancer while reducing expenditures, which will improve cancer-related morbidity and poor quality of life due to delayed diagnosis [2]. The ideal approach to pulmonary nodule management is to avoid unnecessary invasive procedures. A healthcare system report from the United States declared that pulmonary nodules were detected in approximately 25–30% of all chest CT scans between 2006 and 2012, based on which an estimated 1.57 million new pulmonary nodules are detected each year. Only approximately 5% of detected nodules were diagnosed with lung cancer within 2 years [3]. The main goal should be to noninvasively distinguish malignant nodules, which make up 5% of nodules, from the remaining 95% of benign nodules.

Uncertainties regarding follow-up and management of pulmonary nodules should be resolved quickly. There are some risk models and follow-up protocols, but their reliability has not been proven [4]. One of them was developed by the Fleischner Society [1]. In this article, observational experiences from patients with incidental pulmonary nodules detected on CT images in a university hospital managed according to the Fleischner Society are presented.

Aim of the study

The aim of this study was to determine the patient risk factors and nodule characteristics that differentiate benign pulmonary nodules from malignant nodules.

Material and methods

Sample

Patients with pulmonary nodules detected between August 2014 and January 2019 in the Department of Chest Diseases of Akdeniz University were retrospectively analyzed. We included all patients with pulmonary nodules that had been followed according to the Fleischner Society recommendations during the period noted above. All patients were ≥18 years old. Only patients with thin-section (≤1.5 mm) thoracic CT images were included in the study.

Methods

Each patient's age, gender, smoking history, occupational and environmental risk factors, comorbidities, symptoms, follow-up periods, and pathology results of biopsy specimens were obtained from the database. Pulmonary nodules were evaluated by a radiologist. Nodule diameter was calculated as the average of the longest and shortest diameters in the axial, transverse, or coronal section images, whichever was the largest. In patients with multiple nodules, we evaluated the characteristics of the nodules with the largest diameter. The lung localization (peripheral/central localization, right/left lung localization, or lobular localization) and border properties of the nodules were evaluated. Pulmonary nodules that regressed or persisted at follow-up (2-year follow-up for solid nodules, 5-year follow-up for ground-glass nodules) or nodules without evidence of malignancy on biopsy were considered benign. The features of malignant nodules and benign nodules were examined.

Ethics

The study was approved by the Akdeniz University Faculty of Medicine Ethics Committee (date: 01.12.2021, decision no: KAEK-855). The study was conducted in accordance with the Research and Publication Ethics Committee and the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were presented as numbers and percentages for categorical variables and as means, standard deviations, and medians for continuous variables. The Kolmogorov–Smirnov test was used to check whether the data conformed to the normal distribution. Comparisons between groups were made with Fisher's exact test. Data analysis was conducted using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Results

Descriptive data

Twenty-four of the 70 patients with pulmonary nodules did not continue with their follow-up examinations. Six patients did not accept the recommended biopsy, although progression was observed on CT images, and did not continue their follow-up. As a result, there were 40 patients with pulmonary nodules whose final diagnosis could be classified as benign or malignant (Figure 1). The mean age was 63.28±12.06 years. Twenty-two (55%) patients were female. Eleven (27.5%) patients had never smoked, while 29 (62.5%) patients were active or passive smokers.

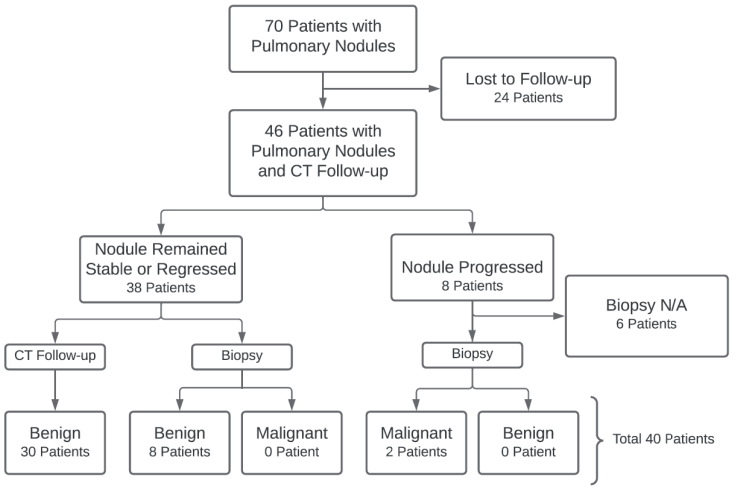

Figure 1. Study flow chart. CT: computerized tomography, N/A: not applicable

Main outcomes

Patient risk factors

Nineteen (47.5%) of the patients were asymptomatic, and their nodules were detected incidentally. Fourteen (35%) patients had chronic obstructive pulmonary disease (COPD), one (2.5%) had interstitial lung disease (ILD), and one (2.5%) had tuberculosis. Occupational and environmental risk factors were present in seven (17.5%) patients. There was a family history of malignancy in six (15%) patients, and four (10%) of those were lung malignancies (Table I).

Characteristics of the nodules

Eight (20%) nodules were solitary, 36 (90%) were solid, 31 (77.5%) were localized in the right lung, and 31 (77.5%) were localized in the right and left upper lobes. The mean nodule diameter was 6.85±3.88 mm. The pulmonary nodules of three (7.5%) patients regressed, while those of 35 (87.5%) patients remained stable, and those of two (5%) patients progressed during follow-up. The progression was significantly higher in men than in women (chi-square: 4.00, p=0.047). There were no significant differences between mean age, smoking characteristics, comorbidities, family history of malignancy, occupational and environmental risk factors, nodule localization, or characteristics of male and female patients (Table II). Lung wedge biopsy was performed in two patients whose nodules progressed and in eight patients with stable nodules. As a result of these biopsies, the two nodules that progressed were diagnosed as malignant, but none of the stable nodules were diagnosed as malignant.

Table I. Gender, age, first visit reasons, and personal and family histories of the patients included in the study.

Variable	Female	Male	Total
n	22	18	40
Age (years)			
Mean	62.11±13.04	64.72±10.94	63.28±12.06
Minimum	24.79	45.72	24.79
Maximum	86.70	86.41	86.70
First Visit Reason Before CT			
Asymptomatic	14	5	19
Symptomatic	8	13	21
Smoking History			
Never smoked	10	1	11
Passive smoker	0	1	1
Active smoker	6	5	11
Ex-smoker	6	11	17
Family Malignancy History			
N/A	12	5	17
No	5	12	17
Yes	5	1	6
Lung malignancy	4	0	4
Comorbidities			
No	5	1	6
Yes	17	17	34
COPD/Asthma	4	10	14
Tuberculosis/ Sarcoidosis/ Granulomatous Disease	0	1	1
Interstitial Lung Disease	0	1	1
Occupational and Environmental Risks			
No	19	14	33
Yes	3	4	7

Age values are presented as mean and standard deviation.

Table II. Characteristics of patients according to nodule course

Variable	Stable/ Regression	Progression	p
n	38	8	
Gender			**0.047[b]**
Female	22	1	
Male	16	7	
Age (years)	63.3±12.36	62.59±7.59	0.878[a]
First Visit Reason Before CT			0.260[b]
Asymptomatic	19	2	
Symptomatic	19	6	
Smoking History			0.577[b]
Never smoked	11	4	
Passive smoker	1	0	
Active smoker	11	1	
Ex-smoker	15	3	
Family Malignancy History			1.000[b]
N/A	23	5	
No	10	2	
Yes	5	1	
Comorbidities			1.000[b]
No	6	1	
Yes	32	7	
Occupational and Environmental Risks			0.176[b]
No	32	5	
Yes	6	3	

Age values are given as mean and standard deviation. The statistically significant value is in bold; [a] independent samples t-test; [b] Fisher's exact test.

When the characteristics of the malignant nodules were examined, both of them were in males who had smoked an average of 40 pack-years. There was no significant difference between the mean ages of patients with benign and malignant nodules (Table III). One of the malignant nodules was a solitary nodule, while the other case had multiple nodules. Both malignant nodules were solid, with irregular borders, and their mean diameter was 7.50±4.95 mm. One of the nodules was located centrally and the other peripherally. One was located in the right lung, and one was located in the upper lobe (Table IV).

When the characteristics of the benign nodules were examined, 24 (57.9%) were women, 27 (71.05%) smoked or used to smoke, and 21 (51%) were asymptomatic (Table III). Thirty-one (81.58%) of the nodules with a benign diagnosis were multiple. Thirty-four (89.47%) nodules were solid, one (2.63%) nodule was ground-glass, and three (7.89%) nodules were subsolid. The mean diameter of the benign nodules was 6.28±3.89 mm. Ten (26.32%) had

Table III. Characteristics of patients according to nodule pathologic diagnosis

Variable	Benign	Malignant	p
n	38	2	
Gender			0.196[b]
Female	22	0	
Male	16	2	
Age (years)	63.30±12.36	63.00±5.13	0.973[a]
First Visit Reason Before CT			0.488[b]
Asymptomatic	19	0	
Symptomatic	19	2	
Respiratory symptom	15	1	
Smoking History			0.924[b]
Never smoked	11	0	
Passive smoker	1	0	
Active smoker	11	0	
Ex-smoker	15	2	

Age values are given as mean and standard deviation; [a] independent samples t-test; [b] Fisher's exact test.

Table IV. Characteristics of nodules according to nodule diagnosis

Variable	Benign	Malign	p
n	38	2	0.364[b]
Solitary	7	1	
Multiple	31	1	
Nodule Diameter	6.82±3.89	7.5±4.95	0.811[a]
Nodule Type			1.000[b]
Solid	34	2	
Non-Solid/ Ground-Glass	4	0	
Subsolid	3		
Ground-Glass	1		
Border Properties			0.085[b]
Smooth	28	0	
Irregular	10	2	
Nodule Localization			1.000[b]
Central	15	1	
Peripheral	24	1	
Right/Left Lung Localization			0.704[b]
Right Lung	29	1	
Left Lung	30	1	
Lobular Localization			0.769[b]
Upper Lobe	29	1	
Middle Lobe	13	0	
Lower Lobe	27	1	

Diameter values are given as mean and standard deviation; [a] independent samples t-test; [b] Fisher's exact test.

irregular borders, 15 (39.47%) were located centrally, 29 (76.32%) were located in the upper lobe, and 30 (78.94%) were located in the left lung (Table IV). When the nodules that were considered benign by clinical radiological follow-up or were diagnosed as benign by biopsy and those diagnosed as malignant by biopsy were compared, there were no significant differences in mean age, gender, smoking history, comorbidities, occupational and environmental risk factors, familial risk factors, or nodule type, localization, size, or border properties.

Discussion

In this study, we did not find any significant differences between benign and malignant nodules for the parameters of mean age, gender, smoking history, comorbidities, occupational and environmental risk factors, familial risk factors or type, localization, size, or border properties. The number, diameter, type, marginal features, and localization, which are related to the probability of a nodule being malignant or benign, were insufficient to make a complete distinction between benign and malignant nodules. We observed in this study that a nodule with a size less than 8 mm could be malignant, or a nodule with irregular borders could be benign. None of these features is an absolutely accurate discriminator. Various guidelines and risk scoring systems have been developed to diagnose malignant nodules, but they are also insufficient and inaccurate for discriminating malignant nodules from benign nodules. Therefore, methods that accurately distinguish a malignant nodule from a benign nodule need to be developed.

Many pulmonary nodules are detected incidentally due to frequent CT imaging for other reasons or for lung cancer screening, which poses a challenge for physicians [5]. Morphological evaluation of the nodule with CT imaging helps distinguish some malignant nodules from benign nodules with high sensitivity and specificity; however, in some cases, it appears that benign and malignant nodules may have similar morphological features. One of the CT features is the localization of the nodule, which is important for the assessment of malignancy risk. Upper lobe localization has been found to increase the risk of malignancy (1.9 times) [6]. In one study, 45% of malignant nodules were localized in the right upper lobe [7]. Although it is known that upper lobe nodules are more likely to be malignant, in our study, 3.23% of upper lobe nodules were malignant, and 30 (96.27%) were benign. Additionally, peripheral or central localization may be associated with the histological subtypes of some malignant nodules. It was previously reported that adenocarsinomas and metastases tend to be peripheral, while squamous cancers tend to be centrally located [8]. In our study, both malignant nodules were adenocarsonomas. One was localized centrally, while the other was localized peripherally.

In addition to localization, the relationship between the size of the nodule and malignancy has been studied extensively, but the study results are conflicting. Davies et al. reported in their study of 150 patients that the mean axial diameters of benign and malignant nodules were 17.7 mm and 20.6 mm, respectively, and they reported that there was no association between nodule diameter and malignancy risk [9]. On the contrary, Yang et al. reported a positive correlation between solitary pulmonary nodule diameter and malignancy [10]. The malignancy risk of solitary pulmonary nodules with a diameter of 5–10 mm was found to be 1.3%, whereas solitary nodules with a diameter less than 5 mm had a malignancy risk of less than 1%, even in high-risk patient groups. Based on this study, the Fleischner Society recommends not following up on nodules smaller than 5 mm [11]. In our study, we observed that there was no significant difference between the diameters of benign and malignant nodules.

The malignancy risk of nodules varies depending on whether they are solid, pure ground-glass, or mixed. The prevalence of malignancy has been reported to be 7–9% in solid nodules, 18–59% in pure ground-glass nodules, and 49–73% in mixed nodules [12,13]. Although the study results are inconsistent, in the largest lung cancer screening study, ground-glass nodules were reported to have the lowest risk of malignancy [14]. Most subsolid nodules are temporary and are caused by infection or bleeding. However, persistent subsolid nodules have often been associated with adenocarcinoma. If subsolid nodules have not disappeared during follow-up, a longer follow-up period (5 years) is recommended due to their slow growth rate [1]. Thirty-six of the nodules in our study were solid, and two of those were malignant. Both malignant nodules in our study were solid.

Malignant nodules are more likely to have irregular lobulated or spiculated margins [15]. It is thought that this border feature is due to the distribution of malignant cells to the pulmonary interstitium. Conversely, benign nodules are expected to have smooth, round border properties. However, there is a significant overlap between the border properties of benign and malignant nodules. In some cases of inflammation/infection, the nodule borders may be irregular, while in some metastatic or primary lung cancers, the nodule borders may be smooth. In our study, we observed that bothmalignant nodules had irregular borders. However, not all the nodules with irregular borders were malignant. Among the benign nodules, approximately one-quarter had irregular margins.

In addition to nodule characteristics, patient risk factors for malignancy should also be included in nodule evaluation. Various patient characteristics have been identified as risk factors for pulmonary malignancy. These include advanced age, female gender, current or previous smoking history, concomitant diseases, such as emphysema and fibrotic lung disease, previous malignancy (thoracic or extrathoracic), previous exposure to asbestos, radium, or uranium, and family history of lung cancer [6]. In our study, there were no significant differences between benign and malignant nodules in terms of mean age, gender, smoking history, comorbidities, occupational and environmental risk factors, or familial risk factors. Both of the patients with malignancies were male.

Limitations

This study has some limitations. The low number of patients included in this study can be considered a limitation. It is thought that studies on larger patient series can contribute to the literature on this subject. The results of positron emission tomography CT were not evaluated in this study. We considered a 2-year follow-up for solid nodules and a 5-year follow-up for subsolid nodules sufficient to decide whether they were benign or malignant, but the adequacy of these periods is still controversial.

Conclusions

In conclusion, a comprehensive clinical history should be obtained from each patient, the risk factors for malignancy should be well established, and the morphological features of the nodules should be carefully evaluated in order to detect malignant pulmonary nodules early and to avoid unnecessary follow-up or invasive sampling methods for benign pulmonary nodules. Despite these factors, there is considerable overlap between benign and malignant nodules, which is a challenge for clinicians.

Ethics Committee Approval: This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the Akdeniz University Medical Faculty Ethical Committee (date: 01.12.2021 decision no: KAEK-855).

References

1. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society. Radiology 2017;284(1):228-243.
2. Loverdos K, Fotiadis A, Kontogianni C, Iliopoulou M, Gaga M. Lung nodules: a comprehensive review on current approach and management. Ann Thorac Med 2019; 14(4):226–238. doi: 10.4103/atm.ATM_110_19.
3. Gould MK, Tang T, Liu IL, et al. Recent trends in the identification of incidental pulmonary nodules. Am J Respir Crit Care Med 2015;192(10):1208–1214. doi: 10.1164/rccm.201505-0990OC.
4. Van Gerpen R. Creating an incidental pulmonary nodule Safety-Net Program. Chest 2021;159(6):2477-2482.
5. Dziadziuszko K, Szurowska E. Pulmonary nodule radiological diagnostic algorithm in lung cancer screening. Transl Lung Cancer Res 2021;10(2):1124-1135.
6. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med 2013;369(10):910-9.
7. Horeweg N, van der Aalst CM, Thunnissen E, Nackaerts K, Weenink C, Groen HJ, et al. Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial. Am J Respir Crit Care Med 2013;187(8):848-54.
8. Chen Y, He X, Shang J, Zhang N, Li X, Liu J, et al. CT findings of pulmonary metastases from primary cardiac angiosarcoma. Curr Med Imaging 2021;17(10):1216-1220.
9. Davies B, Ghosh S, Hopkinson D, Vaughan R, Rocco G. Solitary pulmonary nodules: pathological outcome of 150 consecutively resected lesions. Interact Cardiovasc Thorac Surg 2005; 4(1):18-20.
10. Yang D, Li Y, Liu J, Jiang G, Li J, Zhao H, et al. Study on solitary pulmonary nodules: correlation between diameter and clinical manifestation and pathological features. Chinese Journal of Lung Cancer 2010;13(6):607-11.
11. Bueno J, Landeras L, Chung JH. Updated Fleischner Society guidelines for managing incidental pulmonary nodules: common questions and challenging scenarios. Radiographics 2018; 38:1337-1350.
12. Park CM, Goo JM, Lee HJ, Lee CH, Chun EJ, Im JG. Nodular ground-glass opacity at thin-section CT: histologic correlation and evaluation of change at follow-up. Radiographics 2007;27(2):391-408.
13. Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC, American College of Chest Physicians. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer? ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132(3 Suppl.):94S-107S. doi: 10.1378/chest.07-1352.
14. Li WJ, Lv FJ, Tan YW, Fu BJ, Chu ZG. Pulmonary benign ground-glass nodules: CT features and pathological findings. Int J Gen Med 2021; 14:581-590.
15. Choromanska A, Macura KJ. Evaluation of solitary pulmonary nodule detected during computed tomography examination. Pol J Radiol 2012;77(2):22-34.

Word count: 2229 • Tables: 4 • Figures: 1 • References: 15

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Dirol H, Keven A, Alkan E.
Patient risk factors and nodule characteristics for differentiating benign from malignant pulmonary nodules.
Med Sci Pulse 2023;17(1):32–38. DOI: 10.5604/01.3001.0016.3153

Corresponding author:
Hulya Dirol
Email: hulyadirol@akdeniz.edu.tr
Akdeniz University Hospital, Antalya, Turkey

Other authors/contact:
Ayşe Keven
Email: aysekeven@akdeniz.edu.tr
Ege Alkan
Email: egealkan@akdeniz.edu.tr

Received: 03 August 2022
Reviewed: 14 March 2023
Accepted: 19 March 2023

e-ISSN 2544-1620

Medical Science Pulse 2023 (17) 1

Original papers

Published online: 19 March 2023

DOI: 10.5604/01.3001.0016.3274

THE PHENOMENON OF MEDICAL MARIJUANA: A CROSS-SECTIONAL ANALYSIS OF WARMINSKO-MAZURSKIE VOIVODESHIP PHARMACY DATA

Piotr Engelgardt[1 A, D-F]
• ORCID: 0000-0002-1826-4421

Maciej Krzyżanowski[1 D-F]
• ORCID: 0000-0002-3148-0823

Elżbieta Kuriata[2 B-C]
ORCID: 0000-0002-3301-1465

Grzegorz Kuriata[3 C]
• ORCID: 0000-0003-2762-9530

[1] Department of Pathology and Forensic Medicine, Faculty of Medicine, University of Warmia and Mazury, Olsztyn, Poland

[2] Voivodeship Pharmaceutical Inspectorate, Olsztyn, Poland

[3] Faculty of Mathematics, Physics and Informatics, University of Gdansk, Poland

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Therapy based on medicinal cannabis or medical marijuana has attracted much international attention in recent years.

Aim of the study: To assess the sale of medical marijuana in the Warminsko-Mazurskie Voivodeship between March 2019 and September 2020, estimate medical marijuana demand, and attempt to explain at least some of the reasons for the identified discrepancies.

Material and methods: The study used data on medical marijuana sales in the Warminsko-Mazurskie Voivodeship collected by the Voivodeship Pharmaceutical Inspectorate in Olsztyn.

Results: Medical marijuana is sold in trace amounts in the Warminsko-Mazurskie Voivodeship, although the available data indicate a dynamic increase in sales.

Conclusions: Medical marijuana is available for sale in pharmacies in Poland in the form of pharmaceutical raw material. Currently, its sale, at least in the Warminsko-Mazurskie Voivodeship, is particularly small, though it is very likely that its future sales will increase. Despite this, there are no readily available reliable sources of information in Poland about the known benefits and dangers of medical marijuana use. In this situation, reliable knowledge needs to be disseminated to doctors and patients to safely achieve its therapeutic potential.

KEYWORDS: cannabis, medical marijuana, epidemiology, health policy

Background

Marijuana use for medicinal purposes was prevalent for centuries in numerous cultures globally. However, many drugs containing marijuana were prohibited in the early 20th century, despite no evidence of harmful effects. Preparations of the *Cannabis indica* plant contain many chemical compounds, of which tetrahydrocannabinol (THC) is the best-known psychoactive substance, including approximately 70 cannabinoids (CBDs) and over 400 other biologically active compounds. Indeed, combinations and interactions of these CBDs and other substances, such as terpenoids and fla-

vonoids, result in the therapeutic effects of marijuana [1].

With the advent of work on possible therapeutic applications of medical marijuana (MM), more and more countries have gradually accepted marijuana for medical use in many indications [2,3]. Canada was the first country to legalize MM, which was only possible following court judgments in cases against severely ill people arrested by the police for growing cannabis for personal use [3]. More recently, some jurisdictions in the United States of America (USA) have permitted the use of MM, with the law specifying various medical conditions eligible for a doctor's recommendation. In the states where it is currently available, marijuana is almost exclusively sold in drug emporiums as raw material for smoking. Moreover, individuals with MM cards in Hawaii were initially allowed to cultivate three plants for personal use, though this has recently increased to seven [4].

Other nations have legalized marijuana for medical use, including Australia, the Netherlands, Israel, Germany, and the Czech Republic [3,5,6,7,8]. In Poland, the use of marijuana for medical purposes has been debated for years, with the involvement of the Ministry of Health and the ombudsman. As a result, on 1st November 2017, the Act of the 7th July 2017 amended the Act on Counteracting Drug Addiction and the Act on the Reimbursement of Drugs, Foodstuffs for Particular Nutritional uses and Medical Devices (Journal of Laws item 1458) entered into force [9]. This new law legalized raw materials in the form of herbs, resin, and all non-fibrous hemp extracts for preparing drugs in a pharmacy, which is much cheaper than importing these materials. Under these regulations, Polish patients can access MM products at a local pharmacy and no longer have to apply for products from abroad through direct import [10].

Commissioned by the Polish Ministry of Health on 26th February 2018, the Agency for Health Technology Assessment and Tariffs (AOTiM) issued a negative recommendation on the legitimacy of granting consent for the reimbursement of products containing CBDs for drug-resistant epilepsy, chronic pain (including neoplastic disease, neuropathic pain, and phantom pain), spasticity (including spasticity in multiple sclerosis [MS]), algodystrophy, nausea and vomiting associated with chemotherapy, and MS [11]. Despite this, it should be emphasized that the AOTiM recommendation does not discredit the use of MM but recommends no indications for cost refund from the state budget. Nonetheless, MM became available in Polish pharmacies in January 2019. It was sold as non-refundable preparations for approximately 60-65 Polish Zloty (PLN) per gram, while the price of marijuana on the illegal market at that time was around 50 PLN per gram [12]. Since then, with a break between January and April 2020 due to a change of importer, MM has been available in pharmacies.

MM is defined in Poland as a pharmaceutical raw material intended for the preparation of prescription drugs and "non-fibrous hemp herb and pharmaceutical extracts and tinctures of non-fibrous hemp and non-fibrous hemp resin" [9]. According to this definition, besides weighing portions of the dried plant, prescription drugs such as extracts and tinctures can be prepared.

Initially, only Cannabis sativa L. Red no 2 (trade name of the product), containing 19% THC and >1% CBD, was available. As of October 2020, according to the List of Pharmaceutical Raw Materials [13], six pharmaceutical raw materials intended for the preparation of prescription drugs in a pharmacy are issued to two responsible entities, Aurora Deutschland and Canopy Growth Polska, which include:

- Cannabis flowering tops (flos) from Aurora Deutschland GmbH with 22%THC and 1%CBD.
- Cannabis sativa L. Red No 2
- Cannabis flos from Aurora Deutschland GmbH with 1% THC and 12% CBD.
- Cannabis flos from Aurora Deutschland GmbH with 20%THC and 1% CBD.
- Cannabis flos from Aurora Deutschland GmbH with 8% THC and 8% CBD.
- Cannabis flos from Canopy Growth with 10% THC and 7% CBD.

The list currently includes 18 items sold in packages ranging from 5 to 15 g for the dried preparations and 10 and 30 ml volumes of the extract. These preparations should be taken by vaporization, although the herbs can also be smoked as joints.

It is thought that MM can treat many conditions, the most common of which are epilepsy, pain, spasticity associated with MS, nausea, posttraumatic stress disorder, cancer, cachexia, glaucoma, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), and degenerative neurological conditions [14,15,16,17,18,19,20, 21]. Additionally, MM is potentially efficacious in the treatment of anorexia and weight loss associated with HIV, irritable bowel syndrome, Tourette's syndrome, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia, dementia, traumatic brain injury, addiction, anxiety, depression, sleep disorders, schizophrenia, and other psychoses [14,15,16,17,18,19,20,21]. Moreover, numerous analyses have provided modest evidence of MM efficacy in treating adults with chemotherapy-induced nausea and vomiting, chronic pain, and MS-related spasticity, although short-term use of oral CBDs improves patient-reported spasticity symptoms. However, the effects of CBDs for these conditions are modest, and there is inadequate information on the assessment of their effects in other

conditions [15]. Nonetheless, patients use marijuana to treat medical conditions despite the lack of evidence of its efficacy and often without any information from their doctor [14].

The extensive diseases for which the effectiveness of MM treatment is considered suggests that the population of potential users could be substantial. Indeed, data from the European Cannabis Report shows that the Polish Pharmaceutical Chamber anticipates that up to 300,000 patients in Poland could qualify for medical cannabis [22].

Aim of the study

The purpose of this study was to assess the sale of MM in the Warminsko-Mazurskie Voivodeship between March 2019 and September 2020 and estimate its demand. The study also aimed to explain at least some of the reasons for the discrepancies identified.

Material and methods

This non-experimental study analyzed data on the sale of MM in pharmacies in the Warminsko-Mazurskie Voivodeship between March 2019 and September 2020 (18 months), which was obtained from the Voivodeship Pharmaceutical Inspectorate. The data only provided information on MM sold (in grams) in a given month, with no sensitive information available on specific patients, diseases, or pharmacies.

The Voivodeship Pharmaceutical Inspectorate performs the tasks of State Pharmaceutical Inspection in Poland and complies with the applicable regulations [23]. In this regard, the purpose of the State Pharmaceutical Inspection is to control, inspect, and supervise the quality of marketed medicinal products within the scope defined by the provisions of Pharmaceutical Law and other acts. This involves cooperation with the Pharmacists Union and local Governments to keep relevant registers of pharmacies, wholesalers, manufacturers, and importers of drugs [23].

Results

Estimates suggest that up to 300,000 people may qualify to use MM in Poland, which has approximately 38 million inhabitants [21]. However, the Warminsko-Mazurskie Voivodeship has a population of 1.42 million [24], of which 10,000 to 11,000 patients may need MM at an estimated daily dose of between 0.1 g and 1 g. This translates to around 1 to 10 kg of consumption per day and between 30 and 300 kg monthly. The amounts of MM sold in pharmacies in the Warminsko-Mazurskie Voivodeship from when it became available in the province until September 2020 are shown in Table 1 and Figure 1.

Table 1. The quantity of medical marijuana sold each month between 2019 and 2021 in the Warminsko-Mazurskie Voivodeship

Month	Year	Quantity sold (grams)	Sale Date
3	2019	20	March 2019
4	2019	55	April 2019
5	2019	38	May 2019
6	2019	15	June 2019
7	2019	57	July 2019
8	2019	35	August 2019
9	2019	60	September 2019
10	2019	72	October 2019
11	2019	71	November 2019
12	2019	12	December 2019
1	2020	14	January 2020
2	2020	4,5	February 2020
3	2020	0	March 2020
4	2020	0	April 2020
5	2020	230	May 2020
6	2020	145	June 2020
7	2020	157	July 2020
8	2020	185	August 2020
9	2020	200	September 2020
10	2020	375	October 2020
11	2020	300	November 2020
12	2020	287	December 2020
1	2021	398	January 2021
2	2021	219	February 2021
3	2021	230	March 2021
4	2021	541	April 2021
5	2021	693	May 2021
6	2021	707	June 2021
7	2021	664	July 2021
8	2021	437	August 2021
9	2021	288	September 2021
10	2021	0	October 2021
11	2021	1010	November 2021
12	2021	1166	December 2021

The observed collapse in sales in December 2019 and April 2020 was due to the lack of availability of MM preparations in Poland [25,26,27,28,29,30]. Meanwhile, the significant sales increase in May seems to be a consequence of the prior four-month shortage, as it was not accompanied by a significant long-term upward trend. Therefore, there is no value

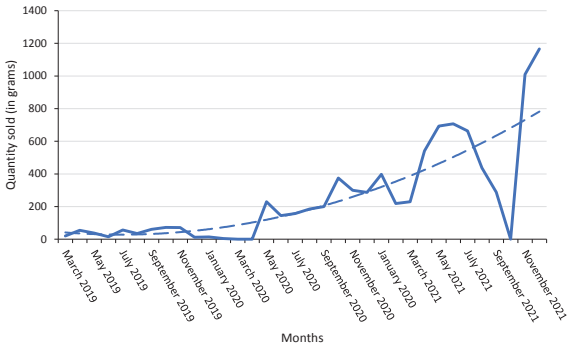

Figure 1. The quantity of medical marijuana sold each month between 2019 and 2021 in the Warminsko-Mazurskie Voivodeship

in comparing the sales in May 2019 to May 2020. On the other hand, a comparison of sales between June and September 2019 to June and September 2020 demonstrates a threefold increase each month. From June to September 2019, 164 g of MM were sold in the Warminsko-Mazurskie Voivodeship, while a year later, this quantity rose more than fourfold to 672 g.

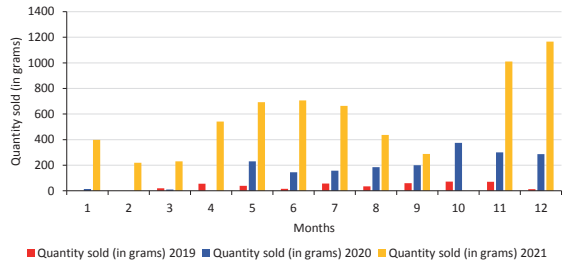

Figure 2. Comparison of medical marijuana sales in corresponding months from 2019 to 2021 in the Warminsko-Mazurskie Voivodeship

Discussion

Comparing the sales level estimated and demanded by the producers with the data presented in this article demonstrates a substantial discrepancy. Even assuming that the estimates adopted by the authors are burdened with a large error, perhaps caused by comparing the population of one Voivodeship with the entire population of Poland, the discrepancy between sales data and estimates is still enormous. Nonetheless, the significant, slightly over 400%, increase in MM sales in comparable months on a year-to-year basis indicates that this difference will probably diminish quickly in the future.

Such a large discrepancy between the estimated demand and current sales values may result from many factors:

1. Errors in estimating the demand.

2. The relatively high cost of therapy in Poland, assuming a price of approximately €10 to €13 per gram, adds up to around €450 per patient per month.

3. The lack of reliable knowledge within society and the medical and pharmaceutical communities about the use of MM results in the substance being treated with great caution.

4. The recent increase in online services offering MM prescriptions, which can be obtained in a short period for a price of more than 100 PLN, after filling out a simple form. In addition, many recreational users continue to buy the product from existing illegal sources due to high prices in the pharmacy trade, while they obtain individual prescriptions to get an alibi for marijuana possession.

The authors are unable to substantively refer to the estimates provided in the sources on the number of patients in Poland who may qualify for the use of MM, and this study did not aim to scrutinize the cost of therapy either. However, the latter warrants a more detailed discussion.

The lack of knowledge regarding MM has been widely emphasized in the literature. For instance, the research of Rogowska-Szadkowska et al. conducted before the legalization of MM in Poland noted that would-be Polish doctors were aware of the medicinal properties of marijuana, though the likelihood that they would demand legal access to it was small. Moreover, they knew little or very little of its benefits, while the media reported almost daily about the dangers of smoking marijuana and illegal plantations [31]. In contrast, research by Braun et al. on the state of knowledge among clinical oncologists in the USA showed that 70% did not feel prepared to make clinical recommendations for MM. The results of these studies suggest that critical gaps remain in MM research, medical education, and policy [32].

A study conducted among Polish doctors in 2020 revealed that more than half of the respondents had never received any education on MM, and more than 90% declared a need to create clear guidelines for using CBDs in practice [33]. In addition, a survey conducted on adult patients in the USA showed that 7% used marijuana for medical purposes often, despite a lack of evidence of efficacy. Meanwhile, every fifth person declaring the use of marijuana for medical reasons had no attending physician, and every third person did not inform their doctor about using marijuana [10].

In Poland, the primary source of MM knowledge is the internet. Therefore, the authors browsed the available Polish-language pages and divided them into websites related to MM importers, vaporizer manufacturers, distributors, or medical clinics offering MM therapy, and sites created by MM enthusiasts. Admittedly, a cursory analysis of the former websites suggests that the information available is consistent with the current knowledge in this area. However, due to the interests of web developers, it is natural to be cautious about their credibility and complete impartiality. Moreover, the sites created by enthusiasts are the

most numerous and popular, with the highest index in Google. These websites often contain general data, highlight the benefits of using MM, have the appearance of professional websites, and refer to scientific data. However, a more careful analysis of the content of these pages often indicates a one-sided presentation of the issue, such as a strong emphasis on the advantages of using MM and concealing or ignoring the risks and negatives of the phenomenon. These pages feature slogans, repeat popular opinions, and sometimes select scientific data or manipulate available knowledge to display only the beneficial aspects of using MM. Thus, the information contained on these web pages should be treated carefully and critically. Unfortunately, no generally available independent websites (not qualifying for either of the categories mentioned above) containing objective information for professionals and interested patients were found. As such, there are no reliable, independent, publicly available sources of up-to-date information or state of knowledge on MM, at least not in Poland.

Even if previous estimates of expected MM sales were to be substantially corrected, an increase in its sale and use should be accounted for, especially in light of the wealth of information, not necessarily reliable, made available in some media campaigns, which may bring about various legal and social consequences. Unfortunately, no reliable and objective assessment of these impacts has been offered yet. In a recently published comprehensive review of the literature on the health and social consequences of decriminalization or legal regulation of drugs, Sheim et al. noticed that research focuses on the USA and on legalizing cannabis. Although many results might be influenced by drug law reform, the current studies maintain a narrow focus and emphasize drug use. However, measures of drug law reform should be better aligned with relevant health and social outcomes [34].

Conclusions

In summary, MM is available for sale in pharmacies in Poland as raw pharmaceutical materials. Currently, at least in the Warminsko-Mazurskie Voivodeship, it is sold in trace amounts, although the available data indicate dynamic increases in sales. Furthermore, future sales of MM will likely continue to increase. Therefore, the expedient dissemination of reliable knowledge on this type of MM among doctors and patients is imperative for the safe use of this potentially therapeutic plant.

Ethics approval and consent to participate

This study contains data based on information from the Voivodeship Pharmaceutical Inspectorate. These data did not reveal sensitive information, such as specific patient details, diseases, or specific pharmacies, and the study was not experimental.

References

1. ElSohly MA, Slade D. Chemical constituents of marihuana: the complex mixture of natural cannabinoids. Life Sci 2005; 78(5):539-548. https://doi.org/10.1016/j.lfs.2005.09.011.
2. Sznitman SR, Bretteville-Jensen AL. Public opinion and medical cannabis policies: examining the role of underlying beliefs and national medical cannabis policies. Harm Reduct J 2015;12:46. https://doi.10.1186/s12954-015-0082-x.
3. Bogdanoski T. Accommodating the medical use of marijuana: surveying the differing legal approaches in Australia, the United States and Canada. J Law Med 2010;17(4):508-31.
4. McKenna GJ. The current status of medical marijuana in the United States. Hawaii J Med Public Health 2014;73(4):105–108.
5. Crowther SM, Reynolds LA, Tansey EM, editors. The medicalization of cannabis. Witness seminar transcript. London: Trustee of the Wellcome Trust; 2010.
6. Stafford N. Seven patients in Germany are granted use of marijuana for medical purposes. BMJ 2009; 20;338:b738.
7. Senthilingam M. Germany joins the global experiment on marijuana legalization [online] [cited 20.01.2023]. Available from URL: http://edition.cnn.com/2016/12/29/health/global-marijuana-cannabis-laws/index.html.
8. Filipková T. Cannabis policy in the Czech Republic. Translational Institute [online] [cited 20.01.2023]. Available from URL: https://www.tni.org/en/article/cannabis-policy-in-the-czech-republic.
9. Ustawa z dnia 7 lipca 2017 r. o zmianie ustawy o przeciwdziałaniu narkomanii oraz ustawy o refundacji leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych [online] [cited 20.01.2023]. Available from URL: http://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20170001458/O/D20171458.pdf. (In Polish).
10. Chromiec Z. Marihuana w gąszczu przepisów. 2018 [online] [cited 20.01.2023]. Available from URL: https://www.medexpress.pl/marihuana-w-gaszczu-przepisow/71401. (In Polish).
11. Agencja Oceny Technologii Medycznych i Taryfikacji (AOTiM). Rekomendacja nr 15/2018 z dnia 26 lutego 2018 r. Prezesa Agencji Oceny Technologii Medycznych i Taryfikacji w sprawie zasadności wydawania zgody na refundację produktów zawierających kannabinoidy: Bedica, Bediol, Bedrolite, Bedrocan, Bedrobinol we wskazaniach: padaczka lekooporna; przewlekły ból (w tym: w chorobie nowotworowej, ból neuropatyczny, ból fantomowy); spastyczność (w tym spastyczność w stwardnieniu rozsianym); algodystrofia; nudności i wymioty związane z chemioterapią; stwardnienie rozsiane [online] [cited 20.01.2023]. Available from URL:https://bipold.aotm.gov.pl/assets/files/zle-

cenia_mz/2017/192/REK/RP_15_2018_kanabinoidy.pdf. (In Polish).

12. Jędrzejczak A. Medyczna marihuana z hurtowni w Łodzi. Cena marihuany w aptece. Gdzie chory kupi konopie? 2019 [online] [cited 20.01.2023]. Available from URL: https://dzienniklodzki.pl/medyczna-marihuana-z-hurtowni-w-lodzi-cena-marihuany-w-aptece-gdzie-chory-kupi-konopie/ar/13840840. (In Polish).
13. Lista Surowców Farmaceutycznych [online] [cited 20.01.2023]. Available from URL: https://rejestrymedyczne.ezdrowie.gov.pl/rpl/lsf. (In Polish)
14. Azcarate PM, Zhang AJ, Keyhani S, Steigerwald S, Ishida JH, Cohen BE. Medical reasons for marijuana use, forms of use, and patient perception of physician attitudes among the US population. J Gen Intern Med 2020;35(7):1979-86. https://doi.org/10.1007/s11606-020-05800-7.
15. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC): National Academies Press (US); 2017 Jan 12. 4, Therapeutic Effects of Cannabis and Cannabinoids [online] [cited 20.01.2023]. Available from URL: https://www.ncbi.nlm.nih.gov/books/NBK423845/.
16. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev 2014; 5(3): CD009270. doi: 10.1002/14651858.CD009270.pub3.
17. Koppel BS, Brust JCM, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of the therapeutic use of medical marijuana (cannabis) in selected neurologic disorders. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82(17):1556-1563 [online] [cited 20.01.2023]. Available from URL: https://n.neurology.org/content/82/17/1556.
18. Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database Syst Rev 2015;12(11):CD009464.https://doi.org/10.1002/14651858.CD009464.pub2.
19. Bridgeman MB, Abazia DT. Medicinal cannabis: history, pharmacology and implications for the acute care setting. PT 2017;42(3):180-8.
20. Lynch ME, Campbell F. Cannabinoids for treatment of chronic noncancer pain: a systematic review of randomized trials. Br J Clin Pharmacol 2011;72:735–44. https://doi.org/10.1111/j.1365-2125.2011.03970.x.
21. The European Cannabis Report™. Prohibition Partners. 2018. [online] [cited 20.01.2023]. Available from URL: https://www.dolcevitaonline.it/wp-content/uploads/2018/07/The3rdEditionoftheEuropeanCannabisReport.pdf.
22. Pascual A. Polish medical cannabis market growing rapidly but remains very small. 2021 [online] [cited 17.12.2021]. Available from URL: https://mjbizdaily.com/polish-medical-cannabis-market-growing-rapidly-but-remains-very-small/.
23. Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne [The Act of September 6, 2001. Pharmaceutical law] [online] [cited 20.01.2023]. Available from URL: https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20011261381/T/D20011381L.pdf.
24. Ludność Polski. Demografia 2020: przyrost naturalny, średni wiek. Prognozy i dane historyczne [online] [cited 20.01.2023]. Available from URL: www.populationof.net. (In Polish).
25. W aptekach brakuje medycznej marihuany. Kiedy trafi do Polski? 2019 [online] [cited 20.01.2023]. Available from URL: https://mgr.farm/aktualnosci/w-aptekach-brakuje-medycznej-marihuany-kiedy-trafi-do-polski/. (In Polish).
26. Kabala D. Jak długo mamy czekać w aptece na lek? Nowy importer konopi, a surowca nadal nie ma. 2020 [online] [cited 20.01.2023]. Available from URL: https://www.marihuana.info.pl/wiadomosci-z-swiata-konopi/jak-dlugo-mamy-czekac-w-aptece-na-lek-nowy-importer-konopi-a-surowca-nadal-nie-ma. (In Polish).
27. Florencka K. Kończy się zapas marihuany w Polsce. Nie wiadomo, kiedy będzie następna dostawa. 2019 [online] [cited 20.01.2023]. Available from URL: https://innpoland.pl/155299,medyczna-marihuana-w-polsce-na-wyczerpaniu-gif-zwleka-z-decyzja. (In Polish).
28. Święchowicz M. „Moja choroba ma sześć etapów. Szósty to samobójstwo. Ja jestem na piątym". A leku nigdzie nie ma. 2020 [online] [cited 20.01.2023]. Available from URL: https://www.newsweek.pl/wiedza/zdrowie/nigdzie-nie-da-sie-kupic-leczniczej-marihuany-a-chorzy-potwornie-cierpia/ezjvqtj. (In Polish).
29. Talar-Śpionek A. Kiedy medyczna marihuana wróci do aptek? 2020 [online] [cited 20.01.2023]. Available from URL: https://www.gdziepolek.pl/blog/kiedy-medyczna-marihuana-wroci-do-aptek. (In Polish).
30. Na rynku aptecznym w Polsce brakuje medycznej marihuany. Powód: brak zgód URPL. 5.10.2021 [online] [cited 20.01.20230]. Available from URL: https://pulsmedycyny.pl/na-rynku-aptecznym-w-polsce-brakuje-medycznej-marihuany-powod-brak-zgod-urpl-1129474. (In Polish).
31. Rogowska-Szadkowska D, Strumiło J, Chlabicz S. Is medical marijuana legalisation possible in Poland? Cent Eur J Public Health 2018;26(1):45-48. https://doi. 10.21101/cejph.a4578.
32. Braun IM, Wright A, Peteet J, Meyer FL, Yuppa DP, Bolcic-Jankovic D, et al. Medical oncologists' beliefs, practices, and knowledge regarding marijuana used therapeutically: a nationally representative survey study. J Clin Oncol 2018;36(19):1957-62. https://doi.org/10.1200/JCO.2017.76.1221.
33. Hordowicz M, Jarosz J, Czaplińska M, Leonhard A, Klimkiewicz A. Polish physicians' perspectives on medical cannabis policy and educational needs: results of on online survey. J Clin Med 2021;10:4545. https://doi.org/10.3390/jcm10194545.
34. Scheim AI, Maghsoudi N, Marshall Z, Churchill S, Ziegler C, Werb D. Impact evaluations of drug decriminalisation and legal regulation on drug use, health and social harms: a systematic review. BMJ Open 2020;10:e035148. http://dx.doi.org/10.1136/bmjopen-2019-035148.

Word count: 2596 • Tables: 1 • Figures: 2 • References: 34

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Engelgardt P, Krzyżanowski M, Kuriata E, Kuriata G.
The phenomenon of medical marijuana: a cross-sectional analysis of Warminsko-Mazurskie Voivodeship pharmacy data.
Med Sci Pulse 2023;17(1):39–45. DOI: 10.5604/01.3001.0016.3274

Corresponding author:
Piotr Engelgardt
Email: piotr.eng@gmail.com
University of Warmia and Mazury, Olsztyn, Poland

Other authors/contact:
Maciej Krzyżanowski
Email: maciej.t.krzyzanowski@gmail.com

Elżbieta Kuriata
Email: elzbietakuriata@wp.pl

Grzegorz Kuriata
Email: grzegorzkuriata12@gmail.com

Received: 26 January 2023
Reviewed: 14 March 2023
Accepted: 19 March 2023

e-ISSN 2544-1620

Medical Science Pulse 2023 (17) 1

Original papers

Published online: 20 March 2023

DOI: 10.5604/01.3001.0016.3207

A PILOT TRIAL EVALUATING STATIC POSTURAL CONTROL AFTER GYM AND POOL EXERCISES IN FEMALES TREATED FOR BREAST CANCER

Aleksandra Bula[1,2 A,B,D-F]
• ORCID: 0000-0002-7457-1506

Julia Stróż[3 A,B,D-F]
• ORCID: 0000-0003-0217-180X

Robert Kwiatkowski[4,5 A]
• ORCID: 0000-0003-2953-7146

Małgorzata Gajda[1 B]
• ORCID: 0000-0002-9028-3395

Dorota Groffik[2 B]
• ORCID: 0000-0002-2266-2457

Wojciech Marszałek[2 C]
• ORCID: 0000-0003-3780-1090

Anna Polak[1 A,C-G]
• ORCID: 0000-0001-6932-5047

[1] Institute of Physiotherapy and Health Sciences, The Academy of Physical Education, Katowice, Poland

[2] Institute of Sport Sciences, The Academy of Physical Education, Katowice, Poland

[3] Student Scientific Association: To be a woman - the importance of physiotherapy and physical activity in gynaecology, obstetrics, and oncology, The Academy of Physical Education, Katowice, Poland

[4] Katowice Oncology Centre, Katowice, Poland

[5] The University Hospital, Krakow, Poland

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Breast cancer (BC) therapies can cause toxic peripheral nerve injury resulting in postural control disorders and increased risk of falling.

Aim of the study: To determine the effects of gym and pool exercises on static postural control in female BC survivors. In this regard, advanced stabilometric parameters, including center-of-foot pressure (COP) excursions, rambling, and trembling, evaluated postural control.

Material and methods: This single group pilot included 11 females (30-65 years) treated for stage II-III BC who completed chemotherapy and/or radiotherapy after breast-sparing surgery or mastectomy. The intervention consisted of two 45-minute exercise sessions in the gym and one 60-minute session in the pool at least once a week for six weeks. Static postural control measurements were recorded with participants standing with eyes open and eyes closed on a force plate, which recorded the range, root-mean-square (RMS), and mean velocity of COP, trembling, and rambling.

Results: The pre-intervention and post-intervention values of stabilometric parameters obtained with eyes closed were not significantly different. However, eyes open measurements showed significant increases in the range, mean velocity, and RMS of COP, the range and RMS of rambling, and the mean velocity of trembling in the medial-lateral direction ($P<0.05$).

Conclusions: The six-week intervention involving gym and pool exercises resulted in static postural control changes in BC survivors. However, the results of this pilot study need to be verified by high-quality randomized clinical trials.

KEYWORDS: breast cancer, physical activity, physical therapy, postural control

Background

Breast cancer (BC) is the most common malignant tumor in females and one of the primary causes of female mortality. In 2018, 2.09 million new female BC cases and 0.63 million deaths were recorded globally [1].

BC therapies involve the risk of health complications, with surgical interventions and radiotherapy leading to muscle injury, tissue necrosis, fibrosis, and scars that deteriorate motor coordination [2,3]. Moreover, chemotherapy-induced peripheral neuropathy (CIPN) disturbs proprioception, motor coordination, muscle strength, and exercise capacity [4], which impairs postural control and increases the risk of falls [5,6,7].

BC prevention and management guidelines underscore the ability of physical activity to positively modulate biological BC risk factors [8,9,10], reduce body mass and estrogenic blood concentration, and increase the level of sex hormone-binding globulin [10]. They are also known to improve adiponectin synthesis and insulin sensitivity, stimulate hepatic and muscle metabolism of fatty acids [8], reduce blood levels of glucose, glycated hemoglobin, and insulin-like growth factor-1 (IGF-1), and increase the concentrations of IGF-binding proteins [9].

Physical exercises improve postural control and reduce the risk of falls in females with BC, although studies in this area are few and use different methodologies. Indeed, only five randomized controlled trials (RCTs) [11-15] and four pilot clinical trials [16-19] have attempted to improve participants' postural control using strength exercises [11], progressive resistance training (of spine and limb muscles) [12], sensorimotor exercises [14], exercises improving postural balance, endurance [15,19], resistance to fatigue [17,18], and upper extremity flexibility [18]. However, only three studies included an all-female BC cohort [14,18,19].

Schwenk et al. [13] divided 22 patients with post-chemotherapy CIPN (only 2 [9.1%] had BC) into two equal groups, an experimental group (EG) and a control group (CG). The EG received interactive game-based balance training 45 minutes per day, twice a week for four weeks, while the CG participants exercised regularly at home. After the intervention, the authors observed significant reductions in hip, ankle, and center of mass sway during standing in a feet-closed-position with eyes open (P=0.010-0.022, except the anterior-posterior [AP] center-of-mass sway) and semi-tandem-position (P=0.008-0.035, except for ankle sway) in the EG.

Vollmers et al. [14] studied 36 females treated for BC, with the EG (n=17) performing sensorimotor exercises twice a week for 12 weeks until the end of therapy and for the following six weeks. Meanwhile, the CG (n=19) performed regular exercises of their choosing at home. Subsequent analysis of static postural control measurements in a standing position with eyes open demonstrated a significantly smaller sway area (cm^2) in a monopedal stance for the EG after chemotherapy (both legs, P<0.001) and six weeks later (left leg, P=0.003; right leg, P<0.001) than the CG. In the bipedal stance, the EG's sway area was significantly smaller than the baseline after chemotherapy compared with the CG (P=0.039).

This pilot trial aimed to determine the effect of gym and pool exercises on static postural balance measured with a force plate in BC-treated females. Similar to other studies, the movement of the center-of-foot pressure (COP) was assessed. However, stabilometric parameters such as the root-mean-square (RMS), rambling, and trembling were measured for the first time in BC survivors.

Aim of the study

The study aimed to determine the effect of gym and pool exercises on static postural control in female BC survivors. Traditional and advanced stabilometric parameters, including COP, rambling, and trembling, evaluated postural control.

Material and methods

Study design

The intervention lasted six weeks and consisted of gym and pool exercises under the supervision of a physiotherapist. The study protocol was prepared to comply with the amended 1964 Declaration of Helsinki and was approved by the Academy's Bioethics Commission. The trial was registered with the Australian-New Zealand Clinical Trials Registry: ANZCTRN12619001599167.

Setting and participants

All participants were treated at the same oncology clinic, and their trial eligibility was assessed against the following inclusion criteria: female, aged 30-65 years, stage II-III BC, underwent breast-sparing surgery or mastectomy and chemotherapy and/or radiotherapy, and consented to participate in the study. The exclusion criteria included contraindications to physical exercise, pregnancy, recurrent BC, and other malignancies and diseases, especially nerv-

ous system and musculoskeletal disorders affecting body balance.

Group allocation

The participants were enrolled in the trial by a physician and informed in writing about its purpose and design and that they could withdraw at any time without prejudice to further treatment.

Patient characteristics and cancer classification

Standard interviews, physical examinations, and medical records provided participant demographic information, and the TNM scale (primary tumor [T], condition of regional lymph nodes [N], distant metastasis [M]) assessed BC type and spread. Meanwhile, a cell proliferation marker (Ki67), estrogen and progesterone receptor status, and epidermal growth factor receptor (EGFr) expression established the biology of the tumor.

Treatment

The participants received BC treatment according to best clinical practice, accounting for the cancer stage and biology, concomitant diseases, and their general condition. Treatment was interdisciplinary and involved surgical intervention, chemotherapy, hormonotherapy, immunotherapy, and radiotherapy.

Breast cancer prevention, education, and psychotherapy

All participants received written information about BC prevention basics and were invited to participate in twelve 45-minute meetings on BC prevention and treatment, delivered twice a week over six weeks. They also participated in peer-group support sessions (eight 45-minute meetings) to reduce their stress and anxiety levels.

Physical activity

The participants exercised twice a week for 45 minutes in the gym and once a week for 60 minutes in the pool for six weeks under the supervision of a specialist cancer physiotherapist. The gym exercises aimed to stretch their chest, back, and shoulder muscles and to improve general fitness and body balance. Each gym session concluded with upper limb relaxation exercises and dynamic breathing exercises performed in standing, sitting, and lying supine positions on the unoperated side, and involved the use of balls, resistance tapes, and gym sticks. The pool exercises aimed to improve postural balance and strengthen their upper and lower limbs and torso muscles and were performed in a standing position, with participants' feet touching or not touching the bottom of the pool, depending on the depth of the water. The gym and pool exercise methodology was derived from the rehabilitation guidelines for females recovering from BC [20].

Stabilographic measurements

Stabilographic measurements utilized a force plate (AMTI, MA, USA), with participants standing quietly, barefoot, and with eyes open or closed. Forces and torques were registered with a sampling frequency of 100 Hz.

The quiet standing tests were performed before the first and after the last training session. During measurements, the participants stood with feet shoulder-width apart, arms hanging at their sides, and their gaze fixated on a mark placed three meters away at eye level. Each measurement (with eyes open and eyes closed) lasted 30 seconds and was repeated three times for reliability.

Calculations employed Matlab r2017b software (Mathworks Inc., MA, USA). The raw COP signal was computed from the registered forces and torques and processed by a low-pass-4th-order Butterworth filter with a 7 Hz cut-off frequency. The COP signal was decomposed using Zatsiorsky and Duarte's method [21] to assess rambling and trembling. The following parameters were calculated and analyzed: mean velocity (V), range (Ra), and RMS of COP, rambling, and trembling.

Outcomes

Primary outcomes

The primary study endpoint measured at week six was static balance control in participants standing with eyes closed. It was assessed based on the Ra, mean V, and RMS of COP, rambling, and trembling in the medial-lateral (ML) and AP directions.

Secondary outcomes

The secondary study endpoint was static postural control measured with eyes open after six weeks of

intervention, assessed against the same set of parameters as the primary outcome.

Statistical analysis

All computations used STATISTICA v.13.1 (StatSoft, Inc., OK, USA). The Shapiro-Wilk test examined variables for normality of distribution, and most data had a non-normal distribution, perhaps due to the small sample size. Consequently, the Wilcoxon signed-rank test compared within-group results obtained pre-intervention and post-intervention. The level of significance was set at $P \leq 0.05$.

Results

Between June 1st, 2019, and November 30th, 2020, 21 females were screened for the trial, with 12 meeting the inclusion criteria for study enrollment. One female (8.33%) withdrew from the intervention due to family problems. Among the remaining 11, nine participated in all training sessions, one missed two gym sessions and one pool session, and one was absent from two sessions, one in the gym and one in the pool. Statistical analysis was performed on data obtained for the 11 participants (Figure 1).

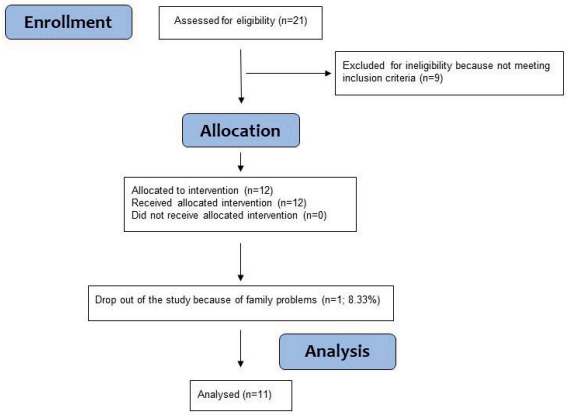

Figure 1. Diagram flow of the study

Patient baseline characteristics

Table 1 outlines the baseline characteristics of the participants. All were Caucasian with a mean age of 57.63±6.42 years (Ra of 41-69) and a mean body mass index (BMI) of 27.36±5.50 kg/m^2. Seven had stage I BC (63.6%), four (36.4%) had stage II BC, and none presented with stage III BC. All participants underwent conserving surgery for BC. Additionally, five (45.5%) had chemotherapy, 10 (90.9%) had radiotherapy, one (9.1%) had immunotherapy, and three (27.3%) had hormonotherapy.

Table 1. Patient characteristics before therapy (n=11)

Characteristics	Experimental group (n=11)
Age [years] (mean ±SD)	57.63±6.42
Range [years]	41–69
BMI [kg/m^2] (mean ±SD)	27.36±5.50
Disease stage [n]	
I	7 (63.6%)
II	4 (36.4%)
III	0 (0%)
Breast surgery type [n]	
Breast conserving surgery	11 (100%)
Chemotherapy [n]	
Yes	5 (45.4%)
No	6 (54.5%)
Time since end of chemotherapy [n]	
<6 months	2 (40%)
6–12 months	3 (60%)
>12 months	0 (0%)
Radiotherapy [n]	
Yes	10 (90.9%)
No	1 (9.1%)
Time since end of radiotherapy [n]	
<6 months	6 (60%)
6–12 months	3 (30%)
>12 months	1 (10%)
Immunotherapy [n]	
Yes	1 (9.1%)
No	10 (90.9%)
Hormonal therapy [n]	
Yes	3 (27.3%)
No	8 (72.7%)

Primary outcome

The primary study outcome was static postural control while standing with eyes closed. The post-intervention tests were not significantly different from the baseline (Table 2).

Secondary outcome

The post-intervention standing with eyes open tests revealed a statistically significant increase in the Ra COP (P=0.004), mean V COP (P=0.026), and RMS COP (P=0.008) in the ML direction. The Ra rambling (P=0.008), RMS (P=0.010), V trembling (P=0.016), and RMS (P=0.041) were also significantly higher. Other changes in the ML direction, including V rambling (P=0.213), Ra trembling (P=0.110), and parameter changes in the AP direction, were non-significant. Table 3 and Figure 2 provide detailed results.

Table 2. Assessment of static posture control with eyes closed

Parameters	Experimental group (n=11)			
	Pre-training	Post-training	p (pre vs. post)	Effect size
Quiet Standing Eyes Closed AP				
Ra COP(cm)	2.39 (1.89–2.65)	2.25 (2.09–2.65)	0.477	0.21
Ra rambling (cm)	1.99 (1.69–2.37)	2.08 (1.85–2.42)	0.424	0.24
Ra trembling (cm)	0.84 (0.78–1.10)	0.97 (0.70–1.36)	0.790	0.08
RMS COP (cm)	0.46 (0.35–0.51)	0.46 (0.38–0.54)	0.374	0.11
RMS rambling (cm)	0.44 (0.32–0.45)	0.41 (0.36–0.53)	0.213	0.06
RMS trembling (cm)	0.09 (0.09–0.15)	0.10 (0.09–0.16)	0.929	0.28
V COP (cm/s)	0.96 (0.82–1.17)	0.98 (0.80–1.19)	0.657	0.20
V rambling (cm/s)	0.67 (0.58–0.83)	0.73 (0.55–0.78)	0.657	0.20
V trembling (cm/s)	0.55 (0.44–0.75)	0.65 (0.41–0.74)	0.929	0.28
Quiet Standing Eyes Closed ML				
Ra COP(cm)	1.44 (0.95–1.78)	1.27 (0.88–1.52)	0.328	0.29
Ra rambling (cm)	1.38 (0.93–1.56)	1.06 (0.78–1.49)	0.248	0.35
Ra trembling (cm)	0.39 (0.30–0.60)	0.45 (0.20–0.48)	0.110	0.48
RMS COP (cm)	0.31 (0.17–0.35)	0.21 (0.16–0.36)	0.328	0.29
RMS rambling (cm)	0.30 (0.17–0.33)	0.19 (0.15–0.33)	0.248	0.35
RMS trembling (cm)	0.04 (0.03–0.07)	0.04 (0.02–0.05)	0.091	0.51
V COP (cm/s)	0.47 (0.36–0.60)	0.49 (0.31–0.59)	0.722	0.11
V rambling (cm/s)	0.37 (0.29–0.46)	0.35 (0.27–0.46)	0.929	0.03
V trembling (cm/s)	0.23 (0.14–0.34)	0.24 (0.09–0.28)	0.534	0.19

Data are presented as median (lower quartile and upper quartile); *p≤0.05; Ra – range; RMS – root-mean-square; V – velocity; COP – center-of-foot-pressure; AP – anterior-posterior; ML – medial-lateral.

Table 3. Assessment of static posture control with eyes open)

Parameters	Experimental group (n = 11)			
	Pre-training	Post-training	p (pre vs. post)	Effect size
Quiet Standing Eyes Open AP				
Ra COP(cm)	1.94 (1.61–2.64)	1.94 (1.39–2.08)	0.091	0.51
Ra rambling (cm)	1.83 (1.44–2.42)	1.70 (1.40–1.91)	0.155	0.43
Ra trembling (cm)	0.59 (0.52–0.80)	0.51 (0.44–0.67)	0.374	0.27
RMS COP (cm)	0.42 (0.30–0.57)	0.38 (0.29–0.44)	0.213	0.38
RMS rambling (cm)	0.41 (0.28–0.52)	0.33 (0.29–0.43)	0.248	0.35
RMS trembling (cm)	0.07 (0.05–0.09)	0.06 (0.04–0.07)	0.328	0.29
V COP (cm/s)	0.65 (0.59–0.75)	0.66 (0.55–0.87)	0.594	0.16
V rambling (cm/s)	0.49 (0.45–0.57)	0.49 (0.44–0.65)	0.534	0.19
V trembling (cm/s)	0.37 (0.25–0.46)	0.34 (0.23–0.49)	0.286	0.32
Quiet Standing Eyes Open ML				
Ra COP(cm)	0.93 (0.85–1.37)	1.30 (0.95–1.75)	0.004*	0.86
Ra rambling (cm)	0.90 (0.78–1.29)	1.14 (0.87–1.70)	0.008*	0.80
Ra trembling (cm)	0.27 (0.15–0.40)	0.44 (0.21–0.52)	0.110	0.48
RMS COP (cm)	0.18 (0.18–0.29)	0.25 (0.20–0.38)	0.008*	0.80
RMS rambling (cm)	0.17 (0.16–0.26)	0.23 (0.18–0.37)	0.010*	0.78
RMS trembling(cm)	0.03 (0.01–0.04)	0.04 (0.02–0.06)	0.041*	0.62
V COP (cm/s)	0.36 (0.27–0.44)	0.47 (0.29–0.62)	0.026*	0.67
V rambling (cm/s)	0.30 (0.23–0.36)	0.32 (0.26–0.41)	0.213	0.38
V trembling (cm/s)	0.16 (0.08–0.19)	0.21 (0.09–0.32)	0.016*	0.72

Data are presented as median (lower quartile and upper quartile); *p≤0.05; Ra – range; RMS – root-mean-square; V – velocity; COP – center-of-foot-pressure; AP – anterior-posterior; ML – medial-lateral.

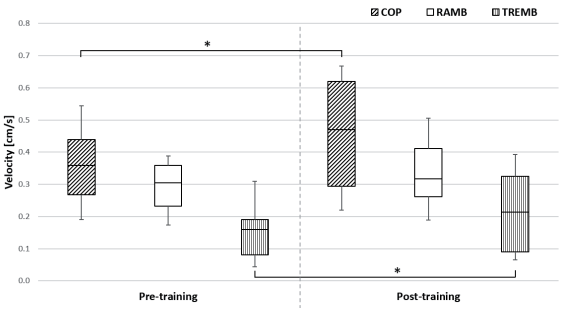

Figure 2. Pre- and post-training velocities for COP, Rambling and Trambling in ML direction

Discussion

Statement and principal findings

Force-plate stabilometry is an advanced method for assessing static and dynamic postural control in people with balance disorders, such as the elderly [22], patients with central nervous system disorders [23], and those with peripheral neuropathies of various etiologies [24,25].

Static postural control is assessed with eyes closed and eyes open, with increased postural sway attributed to the impairment of righting reflexes that need visual, vestibular, and proprioceptive information to function [26]. The cause of increased sway when standing with eyes closed is a proprioceptive rather than a vestibular balance disorder and is concomitant with peripheral neuropathies [27]. Increased postural sway carries a greater risk of a fall when uncontrolled, and controlled sway, even if strong, usually results from a postural response to various motor requirements [28,29].

Müller et al. [30] studied 35 patients with cancer (BC=89%) and 35 healthy persons and confirmed that chemotherapy leads to postural disorders. The postural control parameters did not significantly differentiate the cancer patients before chemotherapy from the controls but were markedly different within cancer patients before and after chemotherapy and between cancer patients after chemotherapy and the CG. The most serious balance problems were observed in participants standing with their eyes closed [30].

Of the three known RCTs [13-15] investigating the effects of physical exercises on static postural control in post-chemotherapy patients, only one [14] studied females treated for BC, and none used a training program similar to this study. Moreover, only one trial [15] assessed postural control using a force plate. The participants included females with CIPN symptoms following treatment for different types of cancer (BC=12 [32.4%]) divided into an EG (n=19) and a CG (n=18). They underwent moderate-intensity endurance training on a stationary bicycle below the individual anaerobic threshold for 30 minutes a day, twice a week, for 12 weeks. Additionally, those in the EG performed balance exercises for 30 minutes per day, twice a week, for 12 weeks. After the intervention, the sway path length of COP in a semi-tandem stance with eyes open was significantly shorter than the baseline in the EG (P=0.018), whereas it did not change in the CG. As a result, the difference between the groups was statistically significant (P=0.049).

Błaszczyk [31] argues that neither increased nor decreased body sway in upright standing is conclusive proof of postural control disorders. Similarly, Portnoy et al. [23] concluded that higher values of stabilometric parameters when standing with eyes open did not necessarily point to postural control problems. They measured and compared static postural control in healthy young adults (n=13; mean age of 25.4±1.1 years), healthy elderly adults (n=11; mean age of 64.5±3.5 years), and adults in a chronic post-stroke state for a period of 6 to 18 months (n=21; mean age of 61.4±10.1 years). The latter had a significantly longer COP path length in quiet standing for 10 seconds with eyes open and eyes closed than all healthy participants, as well as significantly higher maximal COP V, but only when standing with eyes closed. Interestingly, elderly healthy adults had significantly greater COP path length when standing with eyes open but not with eyes closed.

Solnik et al. [32] asked 12 volunteers (aged 28±3 years) to point to objects located in different places and at different distances while standing on a force plate. No association was found between the location of the objects and the body sway indicators, but correlations between comfort ratings and trembling values were significant. The authors [32] concluded that persons performing motor tasks with eyes open focus more on subjective comfort than the amount of postural sway.

According to studies on athletes, there is an association between sport and static postural sway [28,29]. Indeed, Negahban et al. [29] established that athletes in sports requiring dynamic balance, such as taekwondo, had significantly greater postural sway than athletes in sports emphasizing static balance, such as sport shooting. Furthermore, a study on highly-trained karate athletes and untrained physical education students demonstrated that the former had longer COP path lengths, larger rambling and trembling trajectories in the AL direction, and larger rambling trajectories in the ML direction [28].

The cited studies indicate that postural control may depend on factors independent of health disorders. For instance, studies on athletes [28,29] suggest that increased but controlled body sway in a quiet standing with eyes open position may result from adaptation to physical exercise. Similarly, increased body sway in females treated for BC in this study may

signify that the intervention improved their postural control. This observation requires further clinical research to be confirmed.

Limitations

The main limitations of this pilot study were the lack of blinding, the absence of a CG, and the small sample size. In addition, the study did not assess the long-term effects of the intervention. These limitations will be addressed in future clinical trials.

Conclusions

The six-week intervention consisting of two 45-minute exercise sessions in the gym and one 60-minute exercise session in the pool per week did not influence postural control while standing with eyes closed in females treated for BC. Nonetheless, the higher values for some stabilometric parameters measured in the standing with eyes open position, including the Ra, mean V, RMS of COP, Ra rambling and RMS, and mean V of trembling, suggest their postural control may have slightly improved. This observation requires further high-quality RCTs to be confirmed. It is also important to further investigate which physical exercises improve static and dynamic postural control in females treated for BC, how they change their postural sway, and how postural sway relates to their ability to maintain postural balance and reduce the risk of falling.

Abbreviations (listed in the order in which they appear in the article)

BC – breast cancer
RMS – root-mean-square
COP – center-of-foot pressure
CIPN – chemotherapy-induced peripheral neuropathy
IGF – insulin-like growth factor
RCT – randomized controlled trial
V – velocity
Ra – range
ML – medial-lateral
AP – anterior-posterior
BMI – body mass index
EG – experimental group
CG – control group
TMN – tumor node metastasis
EGFr – epidermal growth factor receptor

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2018; 144: 1941-1953.
2. Johansen S, Fosså K, Nesvold IL, Malinen E, Fosså SD. Arm and shoulder morbidity following surgery and radiotherapy for breast cancer. Acta Oncologica 2014; 53: 521-529.
3. Oskrochi R, Shamley D, Lascurain- Aguirrebeña I. Clinical anatomy of the shoulder after treatment for breast cancer. Clinical Anatomy 2014; 27: 467-477.
4. Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. Eur J Cancer 2008; 44: 1507-1515.
5. Tofthagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. Support Care Cancer 2012; 20:583-589.
6. Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. Breast Cancer Res Treat 2016; 159: 327-333.
7. Winters-Stone KM, Horak F, Jacobs PG, Trubowitz P, Dieckmann NF, Stoyles S et al. Falls, functioning and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. J Clin Oncol 2017; 35: 2604-2612.
8. Bouassida A, Chamari K, Zaouali M, Feki Y, Zbidi A, Tabka Z. Review on leptin and adiponectin responses and adaptations to acute and chronic exercise. Br J Sports Med 2010; 44:620-630.
9. Irwin ML, Alvarez-reeves M, Cadmus L, Mierzejewski E, Mayne ST, Yu H, et al. Exercise improves body fat, lean mass, and bone mass in breast ancer survivors. Obesity (Silver Spring) 2009; 17:1534-1541.
10. Verkasalo PK, Thomas H V, Appleby PN, Davey GK, Key TJ. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). Cancer Causes Control 2001; 12:47-59.
11. Twiss JJ, Waltman NL, Berg K, Ott CD, Gross GJ, Lindsey AM. An exercise intervention for breast cancer survivors with bone loss. J Nurs Scholarsh 2009; 41:20-27.
12. Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. J Cancer Surviv 2012; 6:189-199.
13. Schwenk M, Grewal GS, Holloway D, Muchna A, Garland L, Najafi B. Interactive sensor-based balance training in older cancer patients with chemotherapy-induced peripheral neuropathy: a randomized controlled trial. Gerontology 2016; 62:553-563.
14. Vollmers PL, Mundhenke C, Maass N, Bauerschlag D, Kratzenstein S, Röcken C, et al. Evaluation of the effects of sensorimotor exercise on physical and psychological parameters in

breast cancer patients undergoing neurotoxic chemotherapy. J Cancer Res Clin Oncol 2018; 144:1785-1792.

15. Kneis S, Wehrle A, Müller J, Maurer C, Ihorst G, Gollhofer A, et al. It's never too late - balance and endurance training improves functional performance, quality of life, and alleviates neuropathic symptoms in cancer survivors suffering from chemotherapy-induced peripheral neuropathy: results of a randomized controlled trial. BMC Cancer 2019; 19:1-12.

16. Cammisuli S, Cavazzi E, Baldissarro E, Leandri M. Rehabilitation of balance disturbances due to chemotherapy-induced peripheral neuropathy: a pilot study. Eur J Phys Rehabil Med 2016; 52:479-488.

17. Almstedt HC, Grote S, Perez SE, Shoepe TC, Strand SL, Tarleton HP. Training-related improvements in musculoskeletal health and balance: a 13-week pilot study of female cancer survivors. Eur J Cancer Care (Engl) 2017; 26.

18. Foley MP, Hasson SM. Effects of a community-based multimodal exercise program on health-related physical fitness and physical function in breast cancer survivors: a pilot study. Integr Cancer Ther 2016; 15: 446-454.

19. Lee CE, Warden SJ, Szuck B, Lau YKJ. A preliminary study on the efficacy of a community-based physical activity intervention on physical function-related risk factors for falls among breast cancer survivors. Am J Phys Med Rehabil 2016; 95: 561-570.

20. Physical Activity Guidelines Advisory Committee report, 2008. To the Secretary of Health and Human Services. Part A: executive summary. Nutr Rev 2009; 67: 114-20.

21. Zatsiorsky VM, Duarte M. Rambling and trembling in quiet standing. Motor Control 2000; 4: 185-200.

22. Low DC, Walsh GS, Arkesteijn M. Effectiveness of exercise interventions to improve postural control in older adults: a systematic review and meta-analyses of centre of pressure measurements. Sport Med 2017; 47: 101-112.

23. Portnoy S, Reif S, Mendelboim T, Rand D. Postural control of individuals with chronic stroke compared to healthy participants: Timed-Up-and-Go, Functional Reach Test and center of pressure movement. Eur J Phys Rehabil Med 2017; 53: 685-693.

24. Streckmann F, Zopf EM, Lehmann HC, May K, Rizza J, Zimmer P, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. Sports Med 2014; 44: 1289-1304.

25. Duregon F, Vendramin B, Bullo V, Gobbo S, Cugusi L, Di Blasio A, et al. Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: a systematic review. Crit Rev Oncol Hematol 2018; 121: 90-100.

26. Balasubramaniam R, Wing AM. The dynamics of standing balance. Trends Cogn Sci 2002; 6: 531-536.

27. Horak FB. Clinical assessment of balance disorders. Gait Posture 1997; 6: 76-84.

28. Juras G, Rzepko M, Król P, Czarny W, Bajorek W, Słomka K, et al. The effect of expertise in karate on postural control in quiet standing. Arch Budo 2013; 9: 205-209.

29. Negahban H, Aryan N, Mazaheri M, Norasteh AA, Sanjari MA. Effect of expertise in shooting and Taekwondo on bipedal and unipedal postural control isolated or concurrent with a reaction-time task. Gait Posture 2013; 38: 226-230.

30. Müller J, Ringhof S, Vollmer M, Jäger LB, Stein T, Weiler M, et al. Out of balance – postural control in cancer patients before and after neurotoxic chemotherapy. Gait Posture 2020; 77: 156-163.

31. Błaszczyk JW. Sway ratio - a new measure for quantifying postural stability. Acta Neurobiol Exp (Wars) 2008; 68: 51-57.

32. Solnik S, Pazin N, Coelho CJ, Rosenbaum DA, Zatsiorsky VM, Latash ML. Postural sway and perceived comfort in pointing tasks. Neurosci Lett 2014; 569: 18-22.

Word count: 3195 • Tables: 3 • Figures: 2 • References: 32

Sources of funding:
The research was funded by The J. Kukuczka Academy of Physical Education in Katowice.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Bula A, Stróż J, Kwiatkowski R, Gajda M, Groffik D, Marszałek W, Polak A.
A pilot trial evaluating static postural control after gym and pool exercises in females treated for breast cancer.
Med Sci Pulse 2023;17(1):46–54. DOI: 10.5604/01.3001.0016.3207

Corresponding author:
Email: aleksandrabula@gmail.com
The Academy of Physical Education, Katowice, Poland

Other authors/contact:
Julia Stróż
Email: juliastroz11@gmail.com

Robert Kwiatkowski
Email: rkwiat11@wp.pl

Małgorzata Gajda
Email: g.engelmann@awf.katowice.pl

Dorota Groffik
Email: d.groffik@awf.katowice.pl

Wojciech Marszałek
Email: w.marszalek@awf.katowice.pl

Anna Polak
Email: a.polak@awf.katowice.pl

Received: 19 February2023
Reviewed: 15 March 2023
Accepted: 20 March 2023

e-ISSN 2544-1620

Medical Science Pulse 2023 (17) 1

Case report

Published online: 30 March 2023

DOI: 10.5604/01.3001.0053.4019

CONSULTATIONS BETWEEN MIDWIVES AND COUPLES AFFECTED BY INFERTILITY USING THE CREIGHTON MODEL AS A DIAGNOSTIC TOOL FOR HEALTH MONITORING: A CASE REPORT

Woroniecka Weronika[1 A, B, D-F]
• ORCID: 0000-0003-4370-0042

Neneman Marta[2 A,B,D-F]
• ORCID: 0000-0002-9541-4032

Sztyber Beata[2 A,D,E]
• ORCID: 0000-0002-4128-2505

[1] Student of midwifery at the Faculty of Health Sciences, Medical University of Warsaw, Poland

[2] Department of Gynecology and Obstetrics Didactics, Faculty of Health Sciences, Medical University of Warsaw, Poland

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: The Creighton Model is a standardized method of observation based on a couple's knowledge and understanding of the natural processes of the times of fertility and infertility, as well as health indicators. The affliction of infertility is a significant problem and a challenge for modern medicine. There is a need for targeted activities that could provide education in the field of prophylaxis and teach patients how to make procreative decisions. These activities could be undertaken by midwives.

Aim of the study: To introduce the Creighton Model as a tool for monitoring a woman's health and fertility during meetings between infertile couples and midwives, who play a crucial role in emotionally and educationally supporting women and their partners and creating safe conditions for couples during obstetric consultations.

Case report: The patient was a 41-year-old woman who was being treated for infertility for eight years. She has numerous diseases, has undergone several gynecological procedures and operations, and is under constant specialist medical care. Due to a desire to get pregnant, she and her husband follow the recommended treatment, have regular intercourse, and remain in an exclusive relationship.

Conclusions: Use of the Creighton Model can detect abnormalities in the functioning of the body and then treat them. The process of infertility treatment using NaProTechnology includes methods recommended by PTMRiE and SPiN PTGP. Many factors affect the health and fertility of women and couples. Attention should be paid to applying a holistic approach to the patient. The role and presence of the midwife in diagnosis and treatment throughout the infertility process is currently insufficient, and there is room for change. Emotional and educational support, as well as building a sense of security during consultations with a midwife, are of key importance these days.

KEYWORDS: infertility, NaProTechnology, Creighton Model System, midwife visit, interview with infertile couple, health monitoring

Background

Reproductive failures are a serious problem and a challenge for modern medicine. It is a worrying social and demographic phenomenon. Infertility is defined as a condition in which a couple who have regular intercourse and plan to have children do not become pregnant after 12 months [1,2,3,4]. This

condition affects approximately 10–16% of people of reproductive age. In Poland, there are approximately one million infertile couples. However, a lack of knowledge about one's sexuality and fertility can lead to failure to seek diagnosis and treatment [5]. Therefore, there is a need to intensify activities aimed at educating society about infertility prevention, as well as education in the field of reproductive decisions and having a favorable lifestyle. Important in this is both the educational and supportive roles of the midwifery profession, as well as the preventive, health-promoting function for the woman and her family and the caring, diagnostic, and therapeutic functions that are within the purview of midwives. Community midwives could play an important role in this. Many women and couples diagnosed with infertility are burdened by psychological factors, but lifestyle, nutrition, observation of menstrual cycles, and conscious preparation for conception are also factors that can affect fertility. When untreated, the result can be greater psychological burden, more frequent depression, reduced quality of life, and far-reaching social changes.

The article presented here responds to the lack of scientific studies on the topic of the role of midwives during the process of infertility treatment and provides helpful tools for working with infertile couples.

Development of the subject matter, Creighton Model System as a diagnostic tool in partner infertility

Among other roles, the midwife is competent in teaching methods of observing menstrual cycles and analyzing the results of these observations. One of the methods used by couples undergoing infertility treatment is the Creighton Model System.

The Creighton Model is a highly standardized modification of the Billings method. It is based on the couple's knowledge and understanding of the natural processes of fertility and infertility. It is the only system that provides such complete and, at the same time, detailed, standardized information on a woman's procreative ability. The unified and unambiguous markings mean that each instructor of this method and couples using it apply the same symbols and expressions. Using the Creighton Model can also help identify indicators of health and disease in the woman's body.

Three elements are observed in the Creighton Model – development of mucus symptom, menstruation, and noting of so-called "dry days". It has been noticed that the characteristics of cervical discharge secretions change during the menstrual cycle. As ovulation approaches, the elasticity and clarity of the discharge increase, while its viscosity decreases. This provides information about the presence or absence of ovulation. The last day of discharge secretion is called the Peak day.

Cards containing red markers (which indicate days with bleeding), green markers (which indicate dry days), white markers with a baby (which indicate days with mucus), and green markers with a baby (which indicate dry days that are fertile – three consecutive days after the Peak day) are used. On the card, you can also find such markings as the letter P (represents the Peak day and is written on the white tag with the child), the numbers 1, 2, and 3 (which are written on the three consecutive stamps after the Peak day), the letter I (intercourse), and the abbreviation SBP (breast self-examination on the seventh day of the cycle). On the back of the card there is also a key with definitions used during everyday observations [6].

What is important to note is that all observations are made outside the body at the vaginal orifice. During the observation, the following three features are assessed: the sensation that accompanies the wiping of the vaginal orifice with paper, the elasticity and consistency of the secretion, and the color of the secretion. None of these elements can be overlooked or disregarded.

The Creighton Model can serve women and couples not only during the reproductive period but also throughout their procreative life. It is a source of knowledge about a woman's health from puberty to menopause [1,2,3]. The teaching of fertility monitoring could be in the hands of midwives.

Aim of the study

The purpose of the study was to introduce the Creighton Model as a diagnostic tool for obtaining information about a woman's health and fertility status and to learn about the midwife's responsibilities in the care of couples undergoing treatment for infertility.

Material and methods

Care was provided for a woman and her partner who were in the therapeutic process of infertility during the period from September 1st, 2021 to March 31st, 2022. This included an interview with the couple, as well as a retrospective analysis of menstrual cycle observation cards using the Creighton Model from August 11th to December 31st, 2017, an analysis of medical records, their own observations, and an educational conversation with the couple. The process of treating the patient was supplemented with original questions for the interview in the field of

the diagnostic and therapeutic processes of infertility. The couple provided informed consent to provide documentation and participate in the study. The interview, educational conversation, and own observations were carried out via an online conversation using the Zoom communication platform. In December 2021, a one-hour-long online interview was conducted to interview the couple and review their medical records. Subsequently, telephone contact with the patient was maintained in order to expand knowledge about her health condition and to monitor the course of her menstrual cycles. In March 2022, an educational and emotionally supportive meeting was held online for the couple based on a proprietary consultation plan.

Case report

A 41-year-old female patient treated for infertility since 2014 was suffering from endometriosis, polycystic ovary syndrome, insulin resistance, celiac disease, and bipolar disorder. During her infertility treatment, she underwent numerous gynecological procedures and surgeries (hysteroscopy in 2013, 2014, and 2019; laparoscopy in 2015 and 2017) [7]. She is under constant medical care from gynecologists, endocrinologists, and psychiatrists. She also consults with a Creighton Model instructor when needed. She regularly takes medications for her diseases (Glucophage 2000, Medikinet CR, Letrox 75, Acard, ACC, Lametta, and Utrogestan). During infertility diagnostics, *Ureaplasma parvum*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Mycoplasma genitalium* bacteria were identified in her vagina[8]. After repeated antibiotic therapy, no bacteria were found as of 2021. The patient was aware of the need to increase her physical activity, consume a specialized diet, and possibly receive psychological support [9,10,11,12,13].

Due to their desire to become pregnant, she and her husband (41 years old) were applying the recommended treatment, having regular intercourse, and living in an exclusive relationship. The partner was also educated about the factors affecting semen quality [14]. Due to the numerous conditions of the couple, the prognosis for them to conceive was uncertain.

Table 1 presents a proposal for an interview form to be used during a visit conducted by a midwife with a couple during the diagnostic and treatment process of infertility.

Table 1. Interview questions regarding the diagnostic and therapeutic process of infertility

Interview questions regarding the diagnostic and therapeutic process of infertility	
Female – General Information	
Patient's data/name and surname/book number from the patient's medical records:	
Age:	
Past and current chronic diseases, surgeries, and treatments:	
Ailments from individual systems (circulatory, digestive, respiratory, nervous, urinary, joint/muscular, endocrine, sensory organs):	
Regularly taken medications:	
Allergies:	
Blood group:	
Height:	
Body weight:	
BMI:	
Current emotional state:	
Psychological aspects: Have you ever been diagnosed with mental difficulties or have you visited a psychologist, psychotherapist, or psychiatrist? Have you been diagnosed with mental health disorders or psychological diseases, including depression, anxiety, psychoses, and others?	
Family interview	
Presence of diseases in the family (whether there was a problem with infertility among parents or grandparents, as well as heart disease, cancer, other chronic diseases, and genetic diseases):	
Obstetrics interview	
Number of pregnancies:	
Number of miscarriages:	
Births: year, method of pregnancy completion, sex of the child, alive/dead, full-term/not full-term, single or multiple birth, in which week of pregnancy, any diseases and/or developmental and genetic defects diagnosed in the child, whether the child was assessed as healthy after birth:	

Table 1 contd.

Gynecological interview	
First menstruation:	
Nature of the menstrual cycle:	
Cycle duration and regularity:	
Gynecological operations:	
Vaginal biocenosis:	
Diseases relevant to infertility therapy (please enter +/–)	
Endometriosis	
Polycystic ovary syndrome	
Ovarian cysts	
Uterine fibroids	
Urinary incontinence	
Abnormal bleeding	
Soreness during sexual intercourse	
Gynecological cancers (if yes, what kind)	
Irritable bowel syndrome	
Other medical conditions (please specify)	
Male – General Information	
Patient's data/name and surname/book number from the patient's medical records:	
Age:	
Past and current chronic diseases, surgeries, and treatments:	
Ailments from individual systems (circulatory, digestive, respiratory, nervous, urinary, joint/muscular, endocrine, sensory organs):	
Regularly taken medications:	
Allergies:	
Blood group:	
Height:	
Body weight:	
BMI:	
Current emotional state:	
Psychological aspects: Have you ever been diagnosed with mental difficulties or have you visited a psychologist, psychotherapist, or psychiatrist? Have you been diagnosed with mental health disorders or psychological diseases, including depression, anxiety, psychoses, and others?	
Family interview	
Presence of diseases in the family (whether there was a problem with infertility among parents or grandparents, as well as heart disease, cancer, other chronic diseases, genetic diseases)	
Diseases relevant to infertility therapy (please enter +/–)	
Soreness during sexual intercourse	
Tumors of reproductive organs (if yes, what kind)	
Irritable bowel syndrome	
Other diseases (please specify)	
For the couple	
Diagnosis of infertility and observation of menstrual cycles	
Have you been treated for infertility and for how long?	
Did you have children before treatment?	
Did you have children or were you diagnosed with infertility before starting cycle observation with the Creighton Model?	
Why did you start observing cycles using the Creighton Model, and how long have you been observing them?	
Have you used infertility diagnostic methods and, if so, what methods?	
Have you used any methods of infertility treatment? (if yes, what kind)	

Table 1 contd.

Have you/do you use alcohol, cigarettes, or illicit drugs? (if yes, how much and how many times per week)	
Have you used hormonal contraception? (if yes, what kind and for how long)	
Do either of you have jobs where you are exposed to toxic agents? (heavy metals, pesticides, solvents, phthalates)	
Do either of you have a job where you are exposed to ionizing or non-ionizing radiation and high temperature?	
Do either of you do physical work that involves heavy lifting?	
Do either of you have a job where you are exposed to stress?	
Do either of you work shifts, including night shifts? (if yes, on what system)	
Do you play sports? (if yes, please write who does what sport and for how long, how many times per week)	
How often do you eat processed food? (fast food, pizza, ready meals)	
What is the average number of hours of sleep for each of you?	
Have you ever been diagnosed with diseases such as measles, mumps, rubella, and viral parotitis? (if yes, which and in what year)	
Have either of you ever been diagnosed with gonorrhea, chlamydia, or herpes? (if yes, which one and in what year)	
Have either of you been diagnosed with gastric and/or duodenal ulcers?	
Do either of you have high blood pressure?	
Have either of you ever been diagnosed with a hormonal disorder related to a disturbance in the functioning of the pituitary gland, hypothalamus, pancreas, or thyroid gland (hypothyroidism, hyperthyroidism, Hashimoto's disease)?	
Have either of you taken hormonal drugs?	
Have you been diagnosed with obstruction or lack or abnormal anatomy of the vas deferens, fallopian tubes, ovaries, or testicles?	
Have you been diagnosed with anovulation or abnormal levels of any hormones (female and male)?	
Have either of you been diagnosed with an autoimmune disease? (including allergies)	
Have either of you been diagnosed with obesity and/or insulin resistance, diabetes, or heart disease?	
Have you ever been diagnosed with gynecomastia (breast enlargement)?	
Have you ever had genital injuries?	
Have you ever been diagnosed with testicular hydrocele, varicocele, or other genital diseases?	
What advantages do you currently see in observing your cycle using the Creighton Method: is it easy, understandable, helpful?	
What shortcomings do you currently see in observing your cycle using the Creighton Method: is it difficult, perhaps not always clear, does not add anything, or is difficult to interpret?	
What recommendations have you received from the NaProTechnology doctor and cycle instructor or other specialists?	
Interview on the course of observation of menstrual cycles by the couple in the last six months, including whether observations were carried out, whether they were carried out regularly and in detail, the duration and nature of menstrual bleeding observed, the regularity and nature of menstrual cycles, predominant vaginal discharge, and observed changes in subsequent menstrual cycles, with particular emphasis on the last cycle chart.	

Figures 1–4 present the analyzed cards of observation of menstrual cycles of a woman with infertility[6].

In the presented cycle, menstruation lasted nine days. However, it was scanty, which may indicate hormonal disorders. The bleeding was followed by a dis-

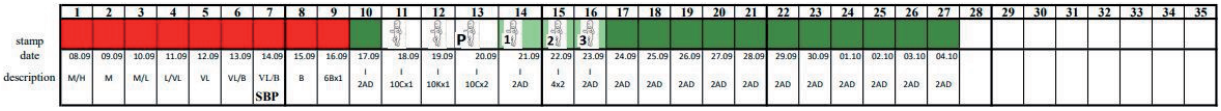

Figure 1. Cycle 8.09-04.10

charge that was moist and unlubricated at first, then very stretchy and white, until it became even more stretchy and transparent. The next day was Peak day. By the end of the cycle, there was not a single dry day but rather a moist and non-lubricating discharge every day.

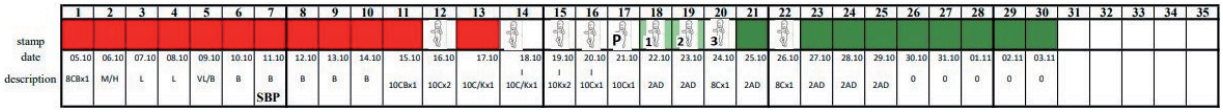

Figure 2. Cycle 5.10-3.11

In this cycle, bleeding lasted 11 days. It was rather meager, which may suggest hormonal disorders. This was followed by a very stretchy discharge that changed from opaque to transparent during the cycle. The last day of discharge occurrence was Peak day, followed by a moist, non-lubricating discharge. The cycle ended with dry days.

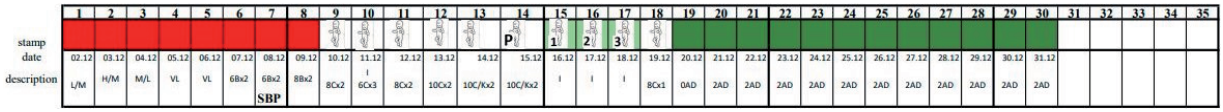

Figure 3. Cycle 4.11-1.12

After eight days of bleeding, a white, medium stretchy discharge was observed, which then turned into a very stretchy and transparent discharge. After Peak day, there was a wet discharge without lubrication, which is considered dry days by the Creighton Model recording standard. Dryness was observed at the end of the cycle. This is the correct cycle.

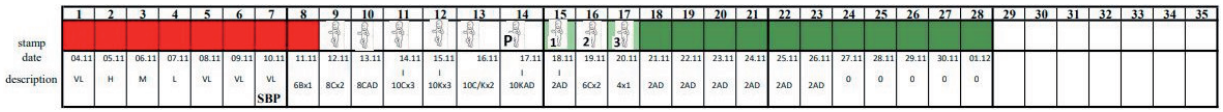

Figure 4. Cycle 2.12-31.12

In this cycle, menstruation lasted eight days. However, it was scanty, which may indicate the presence of hormonal disorders. After the bleeding, a discharge could be observed, which from a little stretchy and opaque became very stretchy and transparent. After Peak day, no discharge was seen, and the woman felt dry. This was followed by an opaque discharge of medium stretchiness, which is abnormal in the post-Peak phase. This may indicate inflammation of the uterus and the presence of bacteria from the *Ureaplasma* and *Mycoplasma* groups.

Table 2 presents the plan for an educational and support meeting conducted online by a midwife with a couple in the process of the diagnosis and treatment of infertility, based on the example of the case described above.

Table 2. Plan of the educational and support meeting in the online form

Plan of the educational and support meeting in the online form
1. Say hello and connect with the couple.
2. Make reference to the last meeting. Clarification of doubts about the couple's answers and updating of test results and the couple's health status.
3. Presentation of the results of the case study along with irregularities in lifestyle and health.
4. A proposal to thoroughly analyze the composition, regularity, and method of preparing meals. Suggesting the creation of a "meal observation diary" in which the patient will record the hours and composition of meals eaten.
5. Due to celiac disease, polycystic ovary syndrome, and insulin resistance, education of the patient in the use of a diet that is limited in cholesterol and saturated fatty acids and rich in fiber. Presentation of relevant products and dishes that meet the above requirements.
6. Due to the lack of physical activity and the occurrence of endometriosis, suggesting that the patient perform regular physical activity. Presentation of ways and places where physical activity can be performed. Conversation with the patient about the forms of enforcing regular physical activity.
7. Patient education in the field of pelvic floor muscle exercises, presentation of example exercises, and people who are specialists in this field. Sensitizing the patient that, due to numerous gynecological surgeries, she is at risk of stress urinary incontinence.
8. Due to numerous hormonal disorders, recommending that the patient have regular contact with a gynecologist-endocrinologist along with regular control of hormone levels.

Table 2 contd.

9. Drawing the patient's attention to further careful observation of cycles due to the risk of cervical inflammation and the presence of hormonal disorders. Conversation with the patient about current control of the level of sex hormones. If necessary, confirmation or clarification of previous medical recommendations in this regard.
10. Conversation with the patient about her experience of trying to conceive. Depending on the needs, providing mental and emotional support. Draw her attention to the importance of conversations between spouses and seeking mutual help.
11. Due to disorders in semen quality, talk with the patient's partner about the factors affecting semen quality.
12. Conversation with the patient about the role of the midwife in the diagnosis of infertility, referring to her personal experience with the midwife.
13. Question time for the couple. Dispel any doubts.
14. Arrange a date for the next meeting.
15. End the conversation.

Discussion

The program used by the couple described in this article stems from "Naprotechnologia". This is the Polish term for the NaProTechnology trademark, which has been registered by the Pope Paul VI Institute dealing with natural fertility planning. It assumes that infertility is caused by a specific reason, and after determining the reason, causal, surgical, or conservative treatment should be applied. It does not include such infertility treatment methods as in vitro fertilization (IVF) or artificial insemination, which are recommended by the Polish Scientific Societies[15,16].

According to the recommendations of PTMRiE and SPiN PTGP, it is recommended to start diagnostics for infertility in women under 35 years of age after one year of regular intercourse without conceiving. A holistic approach to the problem of noticing all elements of biopsychosocial health is recommended. Due to the stress associated with failures in having children[17], psychological consultation should be considered. An important element is also the elimination of harmful factors (improper diet, use of stimulants, smoking, excessive alcohol consumption). It is also important that all activities are aimed at achieving the goal of a normal pregnancy and giving birth to a healthy child[18].

In the standard diagnostic procedure, it is important to determine the cause of infertility and to implement individualized and optimal treatment[19]. To begin with, the function of the ovaries (whether ovulation is occurring), the anatomy of the female reproductive system (whether the fallopian tubes are patent and the structure of the uterine cavity), and semen analysis (assessment of parameters) should be assessed[18,20,21]. In the initial phase of diagnosis, the presented patient was referred for tubal patency testing, ultrasound of the reproductive organs, genetic testing, and basic blood tests, including hormonal tests. The man also had an ultrasound of the reproductive organs, as well as semen quality testing and genetic testing.

When comparing infertility treatment between NaProTechnology and IVF, which is a component of assisted reproductive technology (ART), there are differences between the two methods, but it is also worth considering their commonalities. The use of ART carries the risk of complications for mothers and children. The complications that may occur include, for example, the occurrence of ovarian hyperstimulation syndrome, the presence of multiple pregnancies, and the risk of premature birth, as well as the occurrence of genetic defects in the offspring or future cancer [22,23,24]. The NaProTechnology method focuses on identifying and treating the cause of infertility. In doing so, it improves the patient's gynecological health and restores reproductive function. ART methods involve a huge financial expenditure and uncertain success outcomes. The use of NaProTechnology also involves some financial expenses, but the cost of treatment is much lower. Furthermore, overcoming the cause of infertility allows the couple to conceive again in the future, while the IVF method is designed to produce one pregnancy. If the couple desires to have more children, IVF would once again involve another very large financial expenditure [22,23]. NaProTechnology and ART have the same goal of obtaining a pregnancy and having a healthy baby. However, infertility in about 50% of cases is due to genetic conditions, so conceiving a child through IVF increases the occurrence of harmful genetic variants in the community [23,25]. In NaProTechnology, no such phenomenon occurs.

Among the medical community, there is a noticeable lack of awareness regarding the competence of community midwives. It should be noted that the couple described in this article reported that they had not once interacted with a midwife throughout their entire infertility diagnosis. According to a survey of NaProTechnology patients, as many as 47.52% of those surveyed said they would like to be educated by a midwife about lifestyle, and 40.59% of couples said they would like a midwife to be the person to teach them about monthly cycle observation[26].

In light of the Act on the Profession of Nurses and Midwives, midwives are qualified to educate in the field of preparation for life in the contexts of family, parenthood, fatherhood, and motherhood. They can also teach methods of fertility recognition, educate on the prevention of female diseases and gynecological and obstetric pathologies, and provide advice on nutrition and overall health [26,27]. A primary care midwife, having regular contact with her patients, is able to recognize early fertility problems and direct affected couples to specialists. It seems important to include midwives in the diagnostic and treatment processes of couples burdened with infertility and to competently schedule consultation visits with the infertile couple.

Study limitations

The first limitation of this paper is that it analyzed a single couple. Future work should focus on comparing the diagnostic and therapeutic processes of multiple couples treated for infertility with NaProTechnology using the Creighton Model. Second, this article is based on only a few scientific reports by various authors in peer-reviewed journals and has limited data that could be relied on more confidently regarding tools and ways for midwives to work in infertility clinics. The topic requires further work, but this article nevertheless responds to a certain gap in scientific knowledge on the subject and may be a step toward filling this gap, which seems extremely valuable for the field of infertility.

Conclusions

The Creighton Model is a highly standardized tool for diagnosing infertility. Given the common problem of infertility, it seems important for midwives to become familiar with this tool. In the process of treating infertility, it is also important to pay attention to the holistic approach to the patient, including providing emotional support and promoting a healthy lifestyle. More involvement of midwives with all their competencies to work with infertile couples is an area of possible change in the future. The NaProTechnology program, although not a recommended method of infertility treatment by PTMRiE and SPiN PTGP, but having analyzed the treatment process of the described couple and current recommendations, contains the same elements as other recommended methods [24].

References

1. Hilgers TW. Creighton Model FercilityCare System: autentyczny język zdrowia i płodności kobiety. Warszawa: Fundacja Instytut Rozwoju Położnictwa i Ginekologii; 2012. (In Polish).
2. Stanford JB, Smith KR. Characteristics of women associated with continuing instruction in the Creighton Model Fertility Care System. Contraception 2000; 61(2): 121-9.
3. Hilgers TW, Stanford JB. Creighton Model NaProEducation Technology for avoiding pregnancy. Use effectiveness. J Reprod Med 1998 Jun; 43(6): 495–502.
4. World Health Organization. Multiple definitions of infertility [online] [cited 24.01.2022]. Available from URL: www.who.int/reproductivehealth/topics/infertility/multiple-definitions/en/.
5. Warzecha D, Szymusik I, Pietrzak B, Kosinska-Kaczynska K, Sierdzinski J, Sochacki-Wojcicka N, et al. Sex education in Poland - a cross-sectional study evaluating over twenty thousand polish women's knowledge of reproductive health issues and contraceptive methods. BMC Public Health 2019 Jun 3; 19(1): 689.
6. Hilgers TW. Standardization of teaching. In: The medical and surgical practice of NaProTECHNOLOGYS. Omaha, Nebraska: Pope Paul VI Institute Press; 2004: 57–82.
7. Scheib SA, Thomassee M, Kenner JL. Enhanced recovery after surgery in gynecology: a review of the literature. J Minim Invasive Gynecol 2019 Feb; 26(2): 327–43.
8. Leli C, Mencacci A, Latino MA, Clerici P, Rassu M, Perito S, et al. Prevalence of cervical colonization by Ureaplasma parvum, Ureaplasma urealyticum, Mycoplasma hominis and Mycoplasma genitalium in childbearing age women by a commercially available multiplex real-time PCR: an Italian observational multicentre study. Journal of Microbiology, Immunology and Infection 2018 Apr 1; 51(2): 220–5.
9. Montenegro ML, Bonocher CM, Meola J, Portella RL, Ribeiro-Silva A, Brunaldi MO, et al. Effect of physical exercise on endometriosis experimentally induced in rats. Reproductive Sciences 2019 Jun 19; 26(6): 785–93.
10. Shahid R, Iahtisham-Ul-Haq, Mahnoor, Awan KA, Iqbal MJ, Munir H, et al. Diet and lifestyle modifications for effective management of polycystic ovarian syndrome (PCOS). J Food Biochem 2022 Jul; 46(7): e14117.
11. Walker MH, Tobler KJ. Female Infertility. Treasure Island (FL): StatPearls Publishing; 2023.
12. Walter MH, Abele H, Plappert CF. The role of oxytocin and the effect of stress during childbirth: neurobiological basics and implications for mother and child. Front Endocrinol (Lausanne) 2021; 12: 742236.
13. Sanders KA, Bruce NW. A prospective study of psychosocial stress and fertility in women. Human Reproduction 1997 Oct; 12(10): 2324-9.
14. Koperwas M, Głowacka M. Problem niepłodności wśród kobiet i mężczyzn-epidemiologia, czynniki ryzyka i świadomość społeczna. Aspekty Zdrowia i Choroby 2017; 2(3): 31–49. (In Polish).
15. Tham E, Schliep K, Stanford J. Natural procreative technology for infertility and recurrent miscarriage: outcomes in

a Canadian family practice. Can Fam Physician 2012 May; 58(5): e267-74.
16. Stanford JB, Parnell TA, Boyle PC. Outcomes from treatment of infertility with natural procreative technology in an Irish General Practice. The Journal of the American Board of Family Medicine 2008 Sep 1; 21(5): 375–84.
17. Bożkowa K, Sito A, Chazan B. Niepłodność: opieka zdrowotna nad rodziną. Warszawa: PZWL; 2003: 224. (In Polish).
18. Diagnostyka i leczenie niepłodności – rekomendacje Polskiego Towarzystwa Medycyny Rozrodu i Embriologii (PTMRiE) oraz Polskiego Towarzystwa Ginekologów i Położników (PTGP) [online] 2018 [cited 24.01.2023]. Available from URL: ww.ptmrie.org.pl/pliki/akty-prawne-i-rekomendacje/rekomentacje/Diagnostyka%20i%20leczenie%20niepłodności%20-%20rekomendacje%20PTMRiE%20i%20PTGP%202018.pdf. (In Polish).
19. Kiersnowska I. Comparative analysis of women aged over 35 after in vitro fertilisation and natural fertilisation: a case control study. Medical Science Pulse 2021 Mar 31; 15(1): 1–7.
20. Hilgers TW. Medical risks of infer. In: The medical and surgical practice of NaProTECHNOLOGY. Omaha, Nebraska: Pope Paul VI Institute Press; 2004: 495–508.
21. Pérez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, et al. Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. Human Reproduction 2005 Jun 1; 20(6): 1632–5.
22. Vélez J. R. An ethical comparison between In-Vitro Fertilization and NaProTechnology. The Linacre Quarterly 2012; 79(1): 57–72.
23. Kiani AK, Paolacci S, Scanzano P, Michelini S, et al. Complications related to in vitro reproductive techniques support the implementation of natural procreative technologies. Acta Biomedica: Atenei Parmensis 2020 Nov; 91(13-S): e2020021.
24. Bhandari H, Choudhary M, Stewart J. Complications of assisted reproductive technology treatment and the factors influencing reproductive outcome. Obstet Gynaecol 2018; 20: 177–86.
25. Zorrilla M, Yatsenko AN. The genetics of infertility: current status of the field. Curr Genet Med Rep 2013 Dec 1; 1(4): 10.1007/s40142-013-0027-1.
26. Neneman M, Bączek G, Dmoch-Gajzlerska E. Rola położnej w terapii niepłodności w Polsce w opinii pacjentów [The role of the midwife in the therapy of infertility in Poland in the opinion of patients]. Nursing and Public Health 2019 Mar 29; 9(1): 41–9. (In Polish).
27. Ustawa z dnia 15 lipca 2011 r. o zawodach pielęgniarki i położnej [online] [cited 20.01.2023]. Available from URL: https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20111741039/T/D20111039L.pdf. (In Polish).

Word count: 3797 • Tables: 2 • Figures: 4 • References: 27

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Woroniecka W, Neneman M, Sztyber B.
Consultations between midwives and couples affected by infertility using the Creighton Model as a diagnostic tool for health monitoring: a case report.
Med Sci Pulse 2023;17(1):55–63. DOI: 10.5604/01.3001.0053.4019

Corresponding author:
Weronika Woroniecka
Medical University of Warsaw, Warsaw, Poland
Email: weronika.woroniecka@gmail.com

Other authors/contact:
Neneman Marta
Email: marta.neneman@wum.edu.pl

Beata Sztyber
Email: beata.sztyber@wum.edu.pl

Received: 16 December 2022
Reviewed: 28 March 2023
Accepted: 30 March 2023