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ORIGINAL ARTICLE

THE INFLUENCE OF SENSORY INTEGRATION ON THE LEVEL OF MAINTAINING BALANCE IN CHILDREN WITH MILD INTELLECTUAL DISABILITY

WPŁYW INTEGRACJI SENSORYCZNEJ NA POZIOM UTRZYMANIA RÓWNOWAGI U DZIECI Z UPOŚLEDZENIEM UMYSŁOWYM W STOPNIU LEKKIM

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ABSTRACT

Introduction

The ability to maintain balance is one of the important factors in measuring a person's physical fitness.

Aim

Analysis of the influence of Sensory Integration therapy on maintaining balance in children. Comparison of the study group with the control group of children who performed the author's general development exercises.

Material and methods

The study involved 36 children. The study group consisted of 7 girls and 11 boys who attended Sensory Integration classes. The control group consisted of eight girls and ten boys who performed the author's general development exercises. The age was determined, and the children's weight and height were measured. As part of the study, tests were conducted to assess static balance: the Romberg test with eyes open and closed and the one-legged stance test. Dynamic balance was assessed with a straight-line walking test. All children attended classes once a week for 4 months, and the tests were repeated afterward.

Results

In the study group, after 4 months of therapy, the average results of the tests assessing the vertical body posture in statics and dynamics indicated a significant improvement in maintaining balance ($p < 0.05$). In the control group, after 4 months, the results of the one-legged standing test and the straight-line walking test indicated a significant improvement ($p < 0.0002$, $p < 0.0003$).

Conclusion

The use of Sensory Integration therapy improved the children's balance. Children with normal muscle tone have the best level of balance.

Keywords: balance, sensory integration, general development exercises

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STRESZCZENIE

Wstęp

Zdolność do utrzymania równowagi jest jednym z ważnych czynników pomiaru sprawności fizycznej człowieka (Wang *et al.* 2022).

Cel

Analiza wpływu terapii Integracji Sensorycznej na poziom utrzymania równowagi u dzieci. Porównanie grupy badanej z grupą kontrolną dzieci, które wykonywały autorski zestaw ćwiczeń ogólnorozwojowych.

Materiał i metody

W badaniach udział wzięło 36 dzieci. Grupa badana składała się z 7 dziewczynek 11 chłopców, które uczęszczały na zajęcia Integracji Sensorycznej. Grupa kontrolna liczyła 8 dziewczynek 10 chłopców, które wykonywały autorski zestaw ćwiczeń ogólnorozwojowych. Przed przystąpieniem do terapii, określono wiek, dokonano pomiaru masy oraz wysokości ciała. Przeprowadzono testy oceniające równowagę statyczną: próbę Romberga, test postawy jednonożnej. Równowagę dynamiczną oceniono testem chodzenia po linii prostej. Wszystkie dzieci uczęszczały na zajęcia raz w tygodniu przez okres 4 miesięcy, po tym czasie ponownie przeprowadzono testy.

Wyniki

W grupie badanej po upływie 4 miesięcznej terapii, średnie wyniki testów oceniających pionową postawę ciała w statyce i dynamice wskazywały istotną poprawę utrzymania równowagi ($p < 0,05$). W grupie kontrolnej po upływie 4 miesięcy, wyniki testów stania na jednej nodze oraz testu chodzenia w linii prostej wskazywały znaczącą poprawę ($p < 0,0002$, $p < 0,0003$). Próba Romberga przy oczach otwartych dała w obu grupach jednakowe wyniki w badaniu początkowym oraz brak zmiany po upływie 4 miesięcy.

Wnioski

Pod wpływem zastosowania terapii Integracji Sensorycznej nastąpiła poprawa utrzymania równowagi u dzieci. Dzieci o prawidłowym napięciu mięśniowym charakteryzowały najlepszym poziomem równowagi. Chłopcy wykazywali się lepszym poziomem utrzymania równowagi w porównaniu do dziewczynek.

Słowa kluczowe: integracja sensoryczna, równowaga, ćwiczenia ogólnorozwojowe

Introduction

The upright position of the human body is defined as the vertical positioning of the body about the support plane (Błaszczyk, 2004). This is possible thanks to the equalization of forces and their moments acting on the body; it is a given state of the postural system (Błaszczyk, 2004). Maintaining a vertical posture is possible thanks to the nervous system, which provides tension to the antigravity and postural muscles (Jacobson *et al.,* 2016). As a result of the verticalization of the human body, a complex sensory-reflex process called balance is formed, which develops in the sixteenth week of fetal life (Mucha *et al.,* 2016). The balance system controls sensory impressions between the brain and the human body (Mraz *et al.,* 2010). The main task in maintaining a vertical posture is maintaining the body's center of gravity both in the resting position and in movement (Mucha

et al., 2016). The most important element of the balance system is the vestibular organ, vision, and deep sensation receptors located in muscles, skin, and tendons. Any disorders within these systems cause dysfunctions in maintaining a vertical body posture (Pyda-Dulewicz *et al.* 2016; Gos *et al.* 2019).

The study's main objective was to analyze the effect of Sensory Integration (SI) therapy on the balance of children aged 6–8. Additionally, the effect of SI therapy on children's balance was compared to the control group, which, for various reasons, did not attend classes and, at that time, performed an original set of general development exercises.

Methodology

A total of 36 children (21M, 15F) permanently residing in the Care and Treatment Facility in Jaszkotle participated in the study. SI was used in the study group (11M, 7F), while original general development exercises were implemented in the control group. Children from the control group were excluded from SI mainly due to medical contraindications. In both groups, classes were held once a week for 4 months. The conditions for inclusion in the study were age (6–8 years), balance disorders observed by a physiotherapist, the ability to walk, and mild mental retardation. The conditions for exclusion from the group were: balance disorders caused by diseases or permanent neurological damage, general poor health, lack of cooperation with the child, and mental retardation other than mild. Exercises and tests were performed in an exercise room and a special room for SI therapy in the Children's Care and Treatment Facility in Jaszkotle. Before starting the study, written consent was obtained from the children's legal guardian. Based on medical documentation, the degree of muscle tone was determined among the examined infants. Body weight and height were measured. The static balance was assessed in the studies using:

Romberg tests (eyes open, eyes closed – T1a, T1b, respectively) (Goddard *et al.,* 2015). The following scoring (points) was used: 0 – no changes in posture, the child maintains balance; 1– slight deviation in any direction; 2 – strong swaying and deviation of the upper limbs; 3 – clear loss of balance, raising the arms; 4 – positive test, loss of balance with open and closed eyes, but also when the child maintains balance with open eyes but loses it with closed eyes.

One-legged stance test (T2). According to Goddard Blythe, the scoring (points) was adopted depending on seconds (sec.) below the age norm: 0 points – no abnormalities, 1 point – up to 2 sec., 2 points – up to 4 sec., 3 points – up to 6 sec., 4 points – up to 8 sec. (Goddard Blythe *et al.* 2015).

The Straight Line Walking Test (T3) (Goddard Blythe, 2015) assessed dynamic balance. The following scoring system was used: 0 – no abnormalities, 1 – slight difficulties in maintaining balance, hand and arm movements, change in facial expression, looking down, two symptoms as above (intensity), 3 – body sway, the child is very close to losing balance, 4 – complete loss of balance.

The study group's classes took place in a room adapted for SI therapy. Group 18 was divided into six subgroups of 3 people. The classes took place in an obstacle course containing, among other things, hammocks, suspensions, beams, a climbing wall, and a platform. During the research, an attempt was made to follow the child and not repeat similar task patterns in a short period of time. The exercises in the control group took place in a rehabilitation room. The children performed their general development exercises, and all the classes were held in the form of play. The group of 18 children was also divided into six groups of 3 people each. Each time, the classes had the same pattern: a warm-up, the main part in which the difficulty of the exercises was graded over time, and the final part – a cool-down. In the first month, exercises were performed in sitting and quadruped positions. In the second month, exercises were performed in a standing position, while in the third month, more challenging exercises were used in a standing position;

additionally, an unstable surface was included. In the last month, the children performed balance exercises using an unstable surface, and additionally, exercises with closed eyes were included. After 4 months of therapy, the same tests were performed again to assess the level of maintaining balance in the children.

Results

Main correlations: Basic data and patient characteristics are presented in Table 1. The ages of the children studied ranged from 6 to 9 years. The age distribution in the study and control groups did not differ significantly (p for t test Student is 0.866). Similarly, in the gender structure, body mass, and height of both groups, no statistical significance was observed.

Table 1. Baseline characteristics.

Variable	Study group	Controls
Age (years): Mean ± SD	7.28 ± 0.96	7.22 ± 1.00
Sex:		
Males, n (%) Females, n (%)	11 (61) 7 (39)	10 (56) 8 (44)
Weight (kg)		
MalesMean ± SD Female Mean ± SD	18.8 ± 4.1 21.0 ± 3.3	18.2 ± 3.4 20.1 ± 5.5
Height (cm)		
Males Mean ± SD Female Mean ± SD	110.4 ± 10.1 118.1 ± 7.2	110.1 ± 6.7 113.9 ± 10.5

SD – standard deviation; n – number, % – percent

Detailed results: The tests conducted in the study group before and after the implemented therapy are presented in Table 2, while for the control group, they are presented in Table 3. In the study group, for the remaining tests (T1b, T2, T3) after 4 months of SI use, the average result showed a statistically significant improvement $p < 0.05$ (the average number of points decreased). In the control group, after 4 months of general development exercises, a statistically significant improvement was found in the tests T2 and T3 ($p < 0.05$), except for the Romberg Test with closed eyes (T2) ($p > 0.0679$).

Comparison of therapies (intergroup analysis): Table 4 compares test results between groups based on the therapy implemented (SI vs. general development exercises). Children in both groups performed the Romberg test with open eyes (T1a) flawlessly before and after the implemented therapies ($p = 1.00$). The mean values of balance improvement assessed in tests T1 and T2 did not differ statistically significantly in both groups. In contrast, in test T3, a statistically significant difference was observed, i.e., a "more pronounced" improvement for the control group – general development exercises ($p < 0.05$).

Test results and muscle tone: Table 5 presents the results of balance tests based on the history of muscle tone collected from children's medical records from the neonatal period. It was omitted from the table because all children performed the T1a test without errors. The measurement results refer to all children and are not considered depending on the intention to implement a given therapy. It was found that in the group of 36 children qualified for the study, 16 (44%) showed correct muscle tone, and in 11 (31%), it was increased, and in the remaining 9 (25%) – it decreased. The T2 and T3 results were statistically significant depending on the level of muscle tone, with the best results achieved by children with a history of correct muscle tone and the poorest – with decreased muscle tone.

Discussion

Under the influence of 4 months of SI therapy, there was an improvement in the process

Table 2. The results of examinations in the study group before (Test 1) and after the therapy (Test 2).

Test	Result (pts.)	Cases (n)		Mean (pts.)		Mean difference (B2-B1)	p (Wilcoxon)
		Exam 1	Exam 2	Exam 1	Exam 2		
T1a	0	18	18	0.00	0.00	0	1.0000
T1b	0	12	17	0.33	0.06	−0.28	0.0431
	1	6	1				
T2	0	0	5	2.28	0.94	−1.33	0.0002
	1	3	9				
	2	8	4				
	3	6	0				
	4	1	0				
T3	0	0	1	2.72	1.94	−0.78	0.0010
	1	1	6				
	2	6	6				
	3	8	3				
	4	3	2				

T1a – Romberg test (eyes open), T1b – Romberg test (eyes closed), T2 – UPST, T3 – Walking straight-line test, pts – points

Table 3. The results of examinations in the control group before (Test 1) and after the therapy (Test 2).

Test	Result (pts.)	Cases (n)		Mean (pts.)		Mean difference (B2-B1)	p (Wilcoxon)
		Exam 1	Exam 2	Exam 1	Exam 2		
T1a	0	18	18	0.00	0.00	0	1.0000
T1b	0	12	16	0.33	0.11	−0.22	0.0679
	1	6	2				
T2	0	0	9	2.22	0.83	−1.39	0.0002
	1	4	4				
	2	7	4				
	3	6	1				
	4	1	0				
T3	0	0	5	2.61	1.11	−1.50	0.0003
	1	2	8				
	2	7	4				
	3	5	0				
	4	4	1				

T1a – Romberg test (eyes open), T1b – Romberg test (eyes closed), T2 – UPST, T3 – Walking straight-line test, pts – points

of maintaining balance in children. Rehabilitation using SI methods stimulates the vestibular system and the sense of deep sensation, positively improving children's balance (Przyrowski *et al.* 2013). SI therapy is one of the possible ways of improving children with balance disorders. During classes, there is a massive influx of sensations, especially vestibular and proprioceptive ones, which the child receives, then sorts and triggers a feedback reaction (Pierchała *et al.* 2008). In 2012, very similar studies were conducted on a group of 21 children attending SI classes once a week. Also, after 4 months, balance improved during the exercises, and coordination and accuracy were noted (Shumway-Cook *et al.* 2007). Analysis shows that children with normal muscle tone have the best level of maintaining balance. Children with reduced muscle tone demonstrated the

Table 4. Comparison of the test results between the groups dependent on the therapy.

Test	Mean [pts.]				Mean improvement [pts.]		p (Mann-Whitney)
	Study group		Controls		Study group	Controls	
	Exam 1	Exam 2	Exam 1	Exam 2			
T1a	0.00	0.00	0.00	0.00	0.00	0.00	1.0000
T1b	0.33	0.06	0.33	0.11	0.28	0.22	0.7880
T2	2.28	0.94	2.22	0.83	1.33	1.39	0.8002
T3	2.72	1.94	2.61	1.11	0.78	1.50	0.0046

T1a – Romberg test (eyes open), T1b – Romberg test(eyes closed), T2 – UPST, T3-Walking straight-line test, pts – points

weakest balance. Muscle tone disorders are characterized by difficulties in holding the body against the force of gravity (Matyja *et al.* 1997). A child with reduced muscle tone is characterized by a disorder of the sense of integration between the group of flexors and postural extensors (Matyja *et al.* 1997; Matyja *et al.* 2009). As a result, compensation occurs: the support plane is widened by tilting the pelvis forward (shifting the center of gravity), the feet and knees become valgus, and the spine curves become deeper (Matyja *et al.* 1997; Matyja *et al.* 2009). The entire change in body position causes impairment of postural stability. Thirty-six children participated in our research, of which the average age in the research group was 7.28 years.

In contrast, in the control group, it was 7.22 years, corresponding to intensive psychomotor development. The age distribution in the research and control groups did not differ significantly. The age of 7 is very intensive in terms of development. It is called the golden age of human motor skills (Mraz *et al.* 2010). At the age of 6–7, children reach their first peak of motor skills (Ostrowska *et al.* 1993). At the age of 7–8, the child's body posture is similar to that of an adult; thanks to the growth of the limbs, the abdominal muscles are strengthened, and the body's center of mass is lowered (Kasperczyk, 2000; Kasperczyk, 2004). The studies show that compared to girls, boys achieved results in the T2 and T3 tests, thus demonstrating a better level of maintaining an upright body position. Differences in external structure and gender in children aged 5–12 years, there is no significant relationship between gender and movements of individual body parts during a standing position (Lebiedowska *et al.* 1994; Przyrowski *et al.* 2013). During walking, there was also no difference between the boys and girls aged 5–18 years (Lebiedowska *et al.* 1994; McEvoy *et al.* 2005).

Study limitations

The main limitation of the work is the small number of the study group. Studies should be conducted on a more significant number of people. Additionally, children should be examined for posture defects.

Conclusions

1. The 4-month SI therapy improved the maintenance of balance in children aged 6–8.
2. After 4 months, children achieved better results in the test assessing dynamic balance because of the use of general development exercises.
3. Children with proper muscle tone have the best level of balance.
4. Boys showed a better level of maintaining balance compared to girls.

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ORIGINAL ARTICLE

IMPACT OF SMARTPHONE USAGE ON CERVICAL SPINE PAIN COMPLAINTS

WPŁYW KORZYSTANIA Z TELEFONU KOMÓRKOWEGO NA WYSTĘPOWANIE DOLEGLIWOŚCI BÓLOWYCH KRĘGOSŁUPA SZYJNEGO

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ABSTRACT

Introduction

Mobile phones have become integral to daily life, increasing screen time and contributing to cervical spine pain, possibly due to non-ergonomic posture during smartphone use.

Aim

The study aimed to examine the relationship between cervical spine pain and phone usage time, considering respondents' physical activity levels.

Materials and methods

The survey included 70 respondents (average age 22.4 years). The questions concerned their occupation, cervical spine pain occurrence and intensity (Numerical Rating Scale), physical activity duration and intensity (Modified Borg Rating of Perceived Exertion). Additionally, respondents completed the Neck Disability Index and reported the daily phone usage over the past 14 days according to smartphone system data.

Results

70% of the respondents reported cervical spine pain (average intensity 3.6). Participants used their phones for 5 hours daily on average. 85.7% of the respondents were physicaly activie for 4.6 hours weekly on average, with an average intensity of 2.8. The average Neck Disability Index score was 6.1. No correlation was found between the pain intensity and the phone usage, nor between physical activity duration and intensity. No correlation was found between the Neck Disability Index score and phone usage or physical activity duration and intensity.

Conclusion

Cervical spine pain affects many young people. No relationship was found between phone usage time and pain intensity, but a tendency for longer smartphone usage was observed among individuals with higher Neck Disability Index scores. No impact of physical activity on pain was found. Further studies are needed on a larger group, considering additional factors.

Keywords: pain, mobile phone, cervical spine

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STRESZCZENIE

Wprowadzenie

Telefony komórkowe stały się nieodłącznym elementem codzienności, co spowodowało wydłużenie czasu spędzanego przed ekranem, a tym samym wzrost dolegliwości bólowych w odcinku szyjnym kręgosłupa. Przyczyną tego zjawiska może być nieergonomiczna pozycja ciała podczas użytkowania smartfona.

Cel

Celem badania było zbadanie zależności pomiędzy bólem odcinka szyjnego kręgosłupa oraz czasem używania telefonów, uwzględniając poziom aktywności fizycznej respondentów.

Materiał i metody

Ankieta została wypełniona przez 70 respondentów, średnia wieku wynosiła 22,4 lata. Pytania dotyczyły wykonywanej pracy, występowania i intensywności bólu odcinka szyjnego kręgosłupa (Numerical Rating Scale), czasu i intensywności (Zmodyfikowana Skala Borga) aktywności fizycznej. Ponadto ankietowani wypełnili Neck Disability Index oraz podali dzienny czas korzystania z telefonu z ostatnich 14 dni zgodnie z danymi systemowymi smartphona.

Wyniki

70% respondentów zgłosiło bóle odcinka szyjnego kręgosłupa o średniej intensywności 3,6. Uczestnicy używali telefonu średnio 5 godzin dziennie. 85,7% ankietowanych uprawiało aktywność fizyczną średnio 4,6 godzin w tygodniu ze średnią intensywnością 2,8. Średni wynik kwestionariusza Neck Disability Index wynosił 6,1. Nie wykazano korelacji pomiędzy intensywnością bólu, a czasem użytkowania telefonu oraz intensywnością i czasem wykonywania aktywności fizycznej. Nie wykazano także korelacji pomiędzy wynikami kwestionariusza Neck Disability Index, a czasem użytkowania telefonu oraz intensywnością i czasem wykonywania aktywności fizycznej.

Wnioski

Bóle odcinka szyjnego kręgosłupa dotyczą znaczącej części młodych ludzi. Nie wykazano związku pomiędzy czasem używania telefonu, a odczuwaniem bólu, jednakże zauważono tendencję do dłuższego korzystania ze smartfonów przez osoby z wyższymi wynikami kwestionariusza Neck Disability Index. Nie wykazano także wpływu aktywności fizycznej na dolegliwości bólowe. Konieczne są kolejne badania na większej grupie, uwzględniające dodatkowe czynniki.

Słowa kluczowe: ból, telefon komórkowy, odcinek szyjny kręgosłupa

Introduction

Mobile phones have become an inseparable part of our lives. The multitude of functions and available applications, along with quick access to information, increases the time spent using smartphones. In recent years, cervical spine pain complaints have become one of the most common musculoskeletal issues (Cevik *et al.,* 2020). More and more young people are suffering from these conditions. Students using smartphones most commonly report cervical spine pain (Cevik *et al.,* 2020). Pain results in poorer well-being, decreased quality of life, discourages physical activity, and complicates work tasks (Cevik *et al.,* 2020). While using a phone, the body adopts a non-ergonomic position, with the cervical spine consistently bent forward. Long-term static positions contribute to muscle overload

and the onset of pain, putting significant pressure on spinal structures and causing micro-damages to tissues (Cevik *et al.,* 2020, Alsalameh *et al.,* 2019). Furthermore, cervical lordosis is reduced (Maayah *et al.,* 2023). Some structures are stretched, while antagonistic muscles are contracted. This can lead to postural abnormalities, which may overload other spinal segments and even cause issues with temporomandibular joints (Foltran-Mescollotto *et al.,* 2023). An improper cervical spine position can result in concentration and memory problems, along with headaches (Jung *et al.,* 2024, Delen *et al.,* 2023, Fernández-de-Las-Peñas *et al.,* 2023). Despite the prevalence of pain complaints and frequent smartphone use among young people, there is still a lack of information regarding the relationship between these two factors.

Aim

The aim of the study was to investigate whether there is a relationship between cervical spine pain complaints and smartphone usage time. An additional objective was to explore whether the respondents' level of physical activity influences their perception of cervical spine pain.

Materials

70 respondents (54 women and 16 men, aged 34 ± 2.64 years, range: 19–34) participated in the study. The table below contains data related to the respondents' type of work and/or studies.

Table 1. Characteristics of respondents.

Declared professional activity and/or studies	Amount of people
Work	9
Study	29
Work and study	32

Methodology

Respondents completed an anonymous survey that included sections analyzing phone usage time, physical activity level, and cervical spine pain complaints.

Daily phone usage time was defined based on the "screen time" function of smartphones (available on both Android and iOS). Respondents were asked to provide the "screen time" for the last 14 days. Physical activity was determined through a survey, with questions about the type of physical activity and the hours spent engaging in sports. Activity intensity was defined using the Modified Borg Rating of Perceived Exertion (Scherr *et al.,* 2013). To assess pain intensity, respondents completed the Neck Disability Index, validated in Polish (Guzy *et al.,* 2013). Based on the results of the questionnaire, their level of disability was evaluated, as shown in Table 2. Respondents were also asked to describe the nature and frequency of cervical spine pain. Pain intensity was rated using the Numerical Rating Scale from 0 to 10.

Statistical analysis

The Statistica (13.1) program was used for data analysis.

Shapiro-Wilk's test was used to check for normal distribution. For normally distributed variables, Student's t-test was used, while the Mann-Whitney U test was used for non-normally distributed variables.

The statistical significance threshold was set at $p < 0.05$.

Results

Aggregated analysis of the sample group

According to the survey, respondents spent an average of 5 hours per day using their mobile phones. The minimum reported phone usage time was 1.5 hours per day, and the maximum was 9 hours per day. Respondents' average physical activity time was 4.6 hours per week, with a minimum of 0 hours per week and a maximum of 14 hours per week. The average Neck Disability Index score was 4.1 points,

Table 2. Level of disability based on the number of points scored on the Neck Disability Index questionnaire.

Level of disability	The amount of points scored in the Neck Disability Index questionnaire
No disability	0–4
Mild disability	5–14
Moderate disability	15–24
Severe disability	25–34
Complete disability	35–50

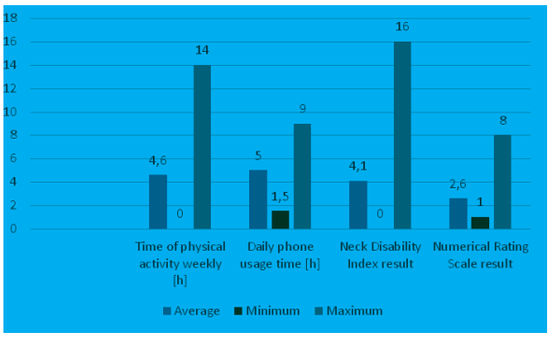

Figure 1. Average time spent using the telephone, time spent being physically active, Numerical Rating Scale subjective pain score and Neck Disability Index questionnaire score among respondents

with a minimum of 0 and a maximum of 16. Pain was rated on average 2.6 on the NRS scale, with scores ranging from 1 to 8.

Respondents' level of disability

Based on the Neck Disability Index results, 26 respondents reported no disability, 42 had mild disability, and 2 had moderate disability. None of the respondents scored in the severe or complete disability range.

Gender variation in results

The time spent using the phone was similar for men and women. Men reported engaging in sports 1.5 hours more per week than women, though this difference was not statistically significant ($p = 0.2371$). Women reported twice as much pain on the Numerical Rating Scale compared to men, and this difference was statistically significant ($p = 0.007$). Women also scored higher on the Neck Disability Index.

Variation in results by duration of phone use

No statistically significant differences in Neck Disability Index scores or Numerical Rating Scale scores were found between respondents who used their phones for less than 4 hours per day and those who used them for 4 hours or more. However, there was a trend towards a higher Neck Disability Index score among those using their phones for more than 4 hours per day.

Variation in results by duration of physical activity

No significant differences were observed between respondents who reported engaging in physical activity for less than 5 hours per week and those who engaged in more than 5 hours per week, either in the Neck Disability Index or Numerical Rating Scale scores.

Relationship of complaints to time of phone use and physical activity

According to the collected data, no correlation was found between cervical spine pain intensity and time spent using the phone or physical activity time.

Table 3. Telephone usage time, physical activity time, Numerical Rating Scale subjective pain score and Neck Disability Index questionnaire score among men and women.

Factor / Daily phone usage time [h]	Repondents whose time using the phone was less than 4 hours		Repondents whose time using the phone was more than 4 hours		Value p
	mean	min. – max.	mean	min. – max.	
Numerical Rating Scale result	2.1	0–7	2.9	0–8	0.1765
Neck Disability Index result	4.2	0–16	6.6	0–15	0.0904

The table shows the mean value, standard deviation (SD) and p-value.

Table 4. Comparison of subjective pain scores according to the Numerical Rating Scale and Neck Disability Index questionnaire scores between those using the phone less than 4 hours a day and respondents using the phone for longer or equally 4 hours a day.

Factor / Gender	Women		Men		Value p
	mean	SD	mean	SD	
Daily phone usage time [h]	4.9	1.6	5.1	2.1	0.6420
Time of physical activity weekly [h]	4.3	2.9	5.9	4.3	0.2371
Numerical Rating Scale result	3	2.1	1.5	2.2	0.007
Neck Disability Index result	6.8	4	5	2.4	0.0161

The table shows the mean, minimum, maximum and p-value.

Table 5. Comparison of subjective pain scores according to the Numerical Rating Scale and the results of the Neck Disability Index questionnaire between those who are physically active less than 5 hours per week and respondents who are physically active equally or more than 5 hours per week.

Factor / Time of physical activity weekly [h]	Respondents whose time doing physical activity was less than 5 hours		Respondents whose time doing physical activity was more than 5 hours		Value p
	mean	min. – max.	mean	min. – max.	
Numerical Rating Scale result	2.8	0–8	2.6	0–7	0.5888
Neck Disability Index result	6.5	1–16	5.6	0–4	0.3282

The table shows the mean value, the range from minimum to maximum value and the p-value.

Table 6. Correlation between time of phone use and physical activity and intensity of cervical spine pain.

Correlation / Factor	Pain intensity	
	value r	value p
Phone usage time	0.0411	0.7357
Time of physical activity	0.117	0.3344

The table shows the r-value and the p-value.

Table 7. Correlation between phone use time and physical activity and Neck Disability Index questionnaire scores.

Correlation / Factor	Neck Disability Index	
	value r	value p
Phone usage time	0.0511	0.6743
Time of physical activity	0.2020	0.0937

The table shows the r-value and the p-value.

No correlation was found between Neck Disability Index scores and time spent using the phone or physical activity time.

For parametric data, Pearson's r correlation coefficient was used, and for non-parametric data, Spearman's rank correlation coefficient was applied.

Discussion

Aggregated analysis of the sample group

This study aims to determine the impact of smartphone use on cervical spine pain among young people.

The average time spent using a phone daily is concerning, amounting to nearly 20% of

the day (5 hours daily). After subtracting sleep time, it approaches 30%. The study by Ayhualem *et al.* showed similar time of phone usage daily (Ayhualem *et al.,* 2021). Young people spend a similar number of hours a day in front of a screen daily as they do on sports activities for an entire week.

Respondents' level of disability

It is surprising that 60% of young, healthy people report a Neck Disability Index score indicative of mild disability. Almost identical results were obtained in the study by Czępińska *et al.* (Czępińska *et al.,* 2024).

Gender variation in results

The literature shows that women are more likely to report complaints of pain than men (Ayhualem *et al.,* 2021, Salameh *et al.,* 2024). Interestingly, our study conduct that women reported twice as much pain as men, despite having similar phone usage times and slightly lower physical activity levels.

Variation in results by duration of phone use

Contrary to expectations, no correlation was found between cervical spine pain intensity and phone usage duration. These results align with other studies (Cevik *et al.,* 2020, Maayah *et al.,* 2023, Foltran-Mescollotto *et al.,* 2021, Alsalameh *et al.,* 2019).

A study of 867 medical students by Maayeh *et al.* found that the number of hours spent using a phone while studying was one of factors that caused cervical spine pain. In addition, it has been shown that the most important factor which influence the experience of cervical spine pain while using the telephone was past trauma to this area (Maayah *et al.,* 2023). It can be assumed that, due to the young age of the respondents and therefore better recovery, the unfavourable position did not have a significant impact on the onset of the complaints (Maayah *et al.,* 2023). In the study by Cevik *et al.* the study group was of a similar age to the above study. They performed MRIs of the cervical spine on all examined patients. The presence of degenerative changes, Modic changes, protrusions or extrusions were assessed and the angle of cervical lordosis was measured. It was shown that people who use the phone for more than three hours a day had statistically significantly more degenerative and Modic-type lesions than those who use the phone for less than three hours a day. Furthermore, prolonged smartphone use was associated with a reduction in cervical lordosis of the spine. These negative changes can be associated with the onset of pain in the cervical spine, increased muscle tension and the occurrence of headaches. Although our study did not show a correlation between the incidence of cervical spine pain and the duration of phone use there was a trend towards a higher disability score according to the Neck Disability Index questionnaire among those using the phone longer. The authors state that degenerative changes of the spine begin to appear after the age of 20 so the age of the respondents may be relevant to the results of the above study, as the majority of respondents are students. Although similar studies have been carried out in different age groups majority of them refer to people of university age. More and more middle-aged and older people use mobile phones and therefore there is a need for more research in higher age groups (Maayah *et al.,* 2023).

In a study of 20 students, there was no correlation that excessive time spent in front of a screen was directly related to the occurrence of cervical spine pain. Despite taking up a position with a flexed cervical spine and head protraction which is negative for joints and soft tissues among young people as in the study conducted there is no effect on the reporting complaints of cervical spine pain (Foltran-Mescollotto *et al.,* 2021).

In a study conducted on a group of medical students, the most common complaint reported in relation to phone use was cervical spine pain. It was shown that students who did not report cervical spine pain were not dependent on phone use (Alsalameh *et al.,* 2019).

Relationship of complaints to time of phone use and physical activity

Our study did not demonstrate an effect of systematic sports activity on the reduction of cervical spine pain. Other studies, despite an age-similar study group, have shown an effect of physical activity on the likelihood of cervical spine pain. They showed that regular exercise reduces the risk of neck discomfort (Salameh *et al.,* 2024, Ayhualem *et al.,* 2021).

Study by Ayhualem *et al.* found a significant effect of breaks during smartphone use on cervical pain. A lack of breaks during phone use increases the likelihood of neck discomfort by as much as 3 times (Ayhualem *et al.,* 2021).

Prevention of pain during phone usage

Nowadays it is impossible to give up the conveniences of mobile phones. It is likely that the time spent in front of the phone will increase so it is important to educate the patient and implement the prevention of cervical spine overload. Changing positions and taking short breaks putting the phone away will be a good recommendation for people who spend a lot of time in front of the screen. In addition, ergonomic principles such as supporting the forearms on a table and positioning the device as close to the eye line as possible can reduce the risk of cervical spine pain (Maayah *et al.,* 2020).

We believe that our results do not prove that there is no effect of the duration of phone use, but reflect the high compensatory capacity of young people. We believe that changes may have a cumulative effect the body increasing the risk of degenerative changes, while this requires a study on an older group as well as long-term prospective studies.

Conclusions

Cervical spine pain is prevalent among a significant portion of young people.

No direct correlation was found between phone usage duration and cervical spine pain, although there was a trend toward higher Neck Disability Index scores among those who used smartphones longer.

Physical activity had no significant impact on cervical spine pain or complaint intensity.

Further research with a larger sample size and consideration of additional factors is necessary.

Declarations

The authors declare no conflicts of interest related to this study.

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ORIGINAL ARTICLE

THE BDNF GENE PROMOTER METHYLATION IN THE COURSE OF ANTIDEPRESSANT TREATMENT IN ADOLESCENT GIRLS WITH FIRST-LIFETIME DEPRESSIVE EPISODE: A PROSPECTIVE STUDY

METYLACJA PROMOTORA GENU BDNF W PRZEBIEGU LECZENIA PRZECIWDEPRESYJNEGO NASTOLATEK Z PIERWSZORAZOWYM EPIZODEM DEPRESJI: BADANIE PROSPEKTYWNE

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ABSTRACT

Introduction

Epigenetic mechanisms regulating the level of BDNF gene expression correlate with achieving remission in the course of Major Depressive Disorder in adults. Studies in this area may contribute to individualization of antidepressant pharmacotherapy and increasing its effectiveness, but the amount of data on this subject in the pediatric population is limited. To date, no study has prospectively investigated changes in the BDNF gene methylation level following antidepressant treatment in adolescents.

Aim

Therefore, we aimed to examine the BDNF gene exon IV promoter methylation status in the group of adolescents treated for the first-lifetime depressive episode. Moreover, we aimed to verify the usefulness of BDNF methylation status as a predictor of treatment outcome.

Material and methods

Our study included 30 female inpatients diagnosed with depression who underwent antidepressant treatment. Before starting treatment and after a minimum of 6 weeks, the level of methylation of the BDNF gene exon IV promoter was examined. Results. No statistically significant difference in the level of BDNF gene methylation before or after treatment was observed, and the usefulness of BDNF gene methylation as a prognostic factor for treatment response was not proven.

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Conclusions
Further studies on a larger group of patients are necessary to verify whether the dynamics of methylation changes in the BDNF gene mirrors the results obtained in adults. Studies on this subject are essential to increase the effectiveness of depression treatment in adolescent patients.

Keywords: mood disorders, depression, adolescence, brain-derived neurotrophic factor, DNA methylation, antidepressant treatment

STRESZCZENIE
Wstęp
Mechanizmy epigenetyczne regulujące poziom ekspresji genu BDNF korelują z osiągnięciem remisji w przebiegu zaburzeń depresyjnych w populacji osób dorosłych. Badania w tym obszarze mogą przyczynić się do indywidualizacji leczenia przeciwdepresyjnego i zwiększenia jego skuteczności, jednakże ilość danych na ten temat jest ograniczona, szczególnie w odniesieniu do populacji pediatrycznej. Do tej pory nie badano prospektywnie zmian w poziomie metylacji genu BDNF w trakcie leczenia przeciwdepresyjnego u nastolatków.

Cel
Celem niniejszego badania jest ocena metylacji promotora egzonu IV genu BDNF w grupie nastolatków leczonych z powodu pierwszego w życiu epizodu depresyjnego oraz weryfikacja przydatności poziomu metylacji BDNF jako predyktora odpowiedzi na leczenie przeciwdepresyjne.

Materiał i metody
Do badania włączono 30 pacjentek hospitalizowanych z rozpoznaniem epizodu depresji, które poddano leczeniu przeciwdepresyjnemu. Przed rozpoczęciem leczenia i po co najmniej 6 tygodniach, oznaczono poziom metylacji promotora egzonu IV genu BDNF.

Wyniki
Nie zaobserwowano statystycznie istotnej różnicy w poziomie metylacji genu BDNF przed lub po leczeniu, a przydatność metylacji genu BDNF jako czynnika prognostycznego odpowiedzi na leczenie nie została udowodniona.

Wnioski
Konieczne są dalsze badania na większej grupie pacjentów, aby zweryfikować, czy dynamika zmian metylacji genu BDNF odzwierciedla wyniki uzyskiwane w badaniach osób dorosłych. Badania w tym obszarze wydają się niezbędne do zwiększenia skuteczności leczenia przeciwdepresyjnego nastolatków.

Słowa kluczowe: zaburzenia nastroju, depresja, nastolatki, neurotroficzny czynnik pochodzenia mózgowego, metylacja DNA, leczenie przeciwdepresyjne

Introduction

Major Depressive Disorder (MDD) is a significant phenomenon among adolescents and adults worldwide. According to the World Health Organization, 14% of the 10–19-year-old experience mental health conditions such as MDD, anxiety disorders, and behavioral

disorders, which are the main root of disabilities and sickness in this age group (WHO, 2021). MDD might lead to suicide attempts which constitute one of the leading causes of death among youth (WHO, 2021). Importantly, meta-analyses show that mental health problems in childhood are strong indicators of mental illness in adulthood (Mulraney *et al.,* 2021). Despite the significant socioeconomic implications of MDD, its pathogenesis is still uncertain, and the treatment outcomes remain unsatisfying. Studies point to the role of gene-environment interactions mediated by epigenetic mechanisms as core mechanisms underlying the emergence of psychiatric disorders, including MDD (Tarapati Rana *et al.,* 2021).

Among many hypotheses addressing the etiopathogenesis of depression, the neurotrophic theory of depression is one of the most frequently investigated. It assumes that environmental stress leads to structural changes in the brain through epigenetic alterations in neurotrophic factors' genes, such as the brain-derived neurotrophic factor (BDNF) gene. Physiologically, brain-derived neurotrophic factor (BDNF) plays a part in both developing and mature brains as it stimulates neurogenesis and eliminates unnecessary neurons (Bathina and Das, 2015). BDNF*'s* low levels are associated with decreased neuroplasticity observed in patients with affective disorders and neurodegenerative diseases. BDNF is mainly expressed in the hippocampus, prefrontal cortex, amygdala, and hypothalamus, which are the brain areas responsible for the emotional and cognitive functions (Bruno Perosa Carniel *et al,* 2021). In support of the neurotrophic theory of depression, researchers report MDD to be associated with diminution of relevant limbic structures, with decreased post-mortem BDNF levels in these brain areas (Duman and Li, 2012).

Nowadays, psychiatry is increasingly striving to personalize treatment methods, which would enable a more effective selection of drugs and, consequently, higher remission rates and a shorter recovery process. The analysis of epigenetic modifications related to neuroplastic processes, such as the methylation of the BDNF gene, is a promising direction in the studies examining biomarkers in MDD (Bathina and Das, 2015). For instance, Kang *et al.* (2013) observed increased BDNF promoter methylation to be associated with the history of suicide attempts among MDD patients (Kang *et al.,* 2013). Additionally, higher methylation status was related to a worse prognosis of the disease course (Kang *et al.,* 2013).

The BDNF gene expression is controlled by nine promoters, each regulating the expression of distinct BDNF transcripts contributing to a region-specific BDNF effect in the brain. BDNF exon IV is expressed differently throughout the development, with transcripts gradually increasing during embryonic and postnatal development and slightly reducing in the adult brain (Aid *et al.,* 2007). Studies on adults show that methylation of the BDNF gene exon IV promoter changes significantly with antidepressant treatment and might serve as a potential predictor of antidepressant treatment response (Molendijk *et al.*, 2011) (Maryna Polyakova *et al.,* 2015) (Webb *et al.,* 2020). To date, no study has investigated changes in the BDNF gene methylation level following antidepressant treatment in adolescents.

Aim

We aimed to analyze prospectively the changes in BDNF gene exon IV promoter methylation status in adolescents treated for the first-lifetime depressive episode. Secondly, we aimed to verify the usefulness of BDNF methylation status as a predictor of treatment outcome.

Material and methods

Ethical Declaration

The study was performed in line with the Declaration of Helsinki and was verified and approved by the Bioethics Committee of the Poznań University of Medical Sciences.

We received written consent to participate in the study from the participants' legal guardians and patients over 13 years of age.

Participants

We recruited patients of the Child and Adolescent Psychiatry Clinic in Karol Jonscher Clinical Hospital in Poznań between January 2021 and April 2023. The inclusion criteria involved age 11–17, admitted with the initial diagnosis of the first episode of depression, no history of psychiatric disease or treatment, no other ongoing somatic disease or medical treatment, no history of addiction or previous organic causes of depressive symptoms. The exclusion criteria involved mental retardation, substance abuse, consent withdrawal, failure to continue treatment throughout the six weeks, and failure to collect blood samples at any of the time points. To qualify for the study, at least a moderate level of depression symptoms must have been present according to ICD-10 which was still an applicable classification in Poland during the recruitment time. According to these criteria, moderate depression requires the presence of at least two core symptoms and at least 3 of the remaining symptoms (Table 1.) for a minimum of 2 weeks (WHO, 1992). The recruitment process has already been described in detail in our previous publication that was based on the same sample of patients (Zwolinska *et al.* 2024).

The diagnosis was established through the patient's examination by the child psychiatrist, weekly observation, and interview with the parent. Participation in the study did not influence the decision-making process regarding the initiation of pharmacotherapy or the type of SSRI. The additional low-dose sedative was introduced among patients with irritability, severe anxiety, and/or insomnia.

Clinical assessment

Patients were qualified and monitored using the Children's Depression Inventory-2 (CDI-2) short form and Hamilton Depression Rating Scale (HDRS). These scales are used both in diagnosing and controlling remission of MDD. The CDI-2 is a self-report used in clinical assessment of depression symptoms in children and adolescents (age 7–17). Results are standardized by the age and sex of patients (Kovacs, 2015). The HDRS is an objective scale that is performed by the psychiatrist. We used HDRS17, which includes 17 assessments about symptoms of depression in the past week, yielding a minimum total score of 0 (least severe) and a maximum score of 52 (most severe). A final score between 0–7 indicates clinical remission (Hamilton, 1960).

BDNF methylation analysis

5 ml of peripheral blood from each fasting participant was collected into EDTA tubes between 7 and 10 a.m. to assess the BDNF

Table 1. Depression criteria according to ICD-10.

Core symptoms	Remaining symptoms
	Loss of confidence or self-esteem
	Unreasonable feelings of self-reproach or guilt
Depressed mood	Recurrent thoughts of death or suicide
Loss of interest	Diminished ability to think/concentrate or indecisiveness
Reduction in energy	Change in psychomotor activity with agitation or retardation
	Sleep disturbance
	Change in appetite with weight change

Treatment with selective serotonin reuptake inhibitor (SSRI) - sertraline or fluoxetine – was introduced based on clinical indications included in the NICE guidelines (NICE, 2019).

exon IV promoter methylation using quantitative methylation-specific real-time PCR (qMS-PCR). Two versions of the primers were created based on DNA sequence regions that

obtained the promoter region of exon IV (27.722.850 – 27.723.477 Homo sapiens chromosome 11, GRCh37.p13). The primers were designed with Methyl Primer Express™ Software v1.0 (Applied Biosystems, Waltham, MA, USA). We performed the analysis using the primer described in Table 2. Isolated genomic DNA and CpGenome Human Methylated & Non-Methylated DNA Standard Set (Sigma-Aldrich, Merck KGaA, Darmstadt, Germany) was converted using a sodium bisulfite kit. Chemical modification of 500 ng of genomic DNA and standards was performed using an EZ DNA Methylation Gold Kit™ (Zymo Research, Irvine, CA, USA). After sodium bisulfite conversion, the percentage of methylation index (MI) was assessed by qPCR with two pairs of primers for the methylated and unmethylated promoter region of the BDNF gene with FastStart Essential DNA SYBR Green Master (Roche, Basel, Switzerland). The MI, expressed as a percentage of gene methylation (MI – %), was calculated for each sample using the following formula: $MI = [1/(1 + 2^{-(CtU-CtM)})] \times 100\%$, where CtM and CtU are derived from qMSP with primers for the methylated and unmethylated gene sequences, respectively.

Statistical analysis

Statistical analysis was executed using PQStat Software version 1.8.2.238. The distribution of the variables was studied using the Shapiro-Wilk Test. Since our data did not follow normal distribution, the Wilcoxon Test was performed to compare paired samples, and the Mann-Whitney Test was used for independent groups. The nominal variables were compared through the Chi-Squared Test. The logistic regression was performed to analyze the correlation between initial MI and treatment outcome, including the potential confounding factors (age, BMI, depression severity, time of treatment). The significance level was set at $\alpha < 0.05$ for all analyses.

Results

Recruitment and clinical characteristics

Forty-nine patients met the inclusion criteria. Fifteen patients were excluded due to lack of consent to participate in the study/lack of compliance in taking the medication/lack of follow-up assessment after treatment. Finally, thirty-four patients were included in the study: thirty girls and four boys. Given the significant gender disproportion, only female patients were finally accepted in the analysis as a studied group.

Table 2. Primers sequence (the 5' to 3' direction).

Forward Methylated DNA (MF)	Reverse Methylated DNA (MR)	Forward Unmethylated DNA (UF)	Reverse Unmethylated DNA (UR)
AGCGAGAGTAGTTTTTTTCGC	CATATAACAACGCACGTCAAA	GGTAGTGAGAGTAGTTTTTTTTGT	TCATATAACAACACACATCAAAAC

Study protocol

The clinical (CDI-2 and HDRS) and molecular (BDNF exon IV promoter MI) analyses were conducted twice: before introducing antidepressant treatment (t0) and after a minimum of six weeks after initiation (t1). Based on the CDI and HDRS results at t1, the patients were classified as, responders' or, non-responders'. To be classified as a, responder,' a minimum 50% reduction in symptoms in both HDRS and CDI-2 must have been present or HDRS result < 7.

The characteristics of the patients are presented in Table 3. All of them were females, aged 11–16, of Caucasian origin. The period of antidepressant treatment ranged from six to eleven weeks. 57% of participants received sertraline, and 43% fluoxetine. 17 patients required additional sedative treatment with quetiapine/chlorprotixene/trazodone/hydroxyzine /risperidone/melatonin. 13 individuals responded to the introduced treatment and were classified as 'responders'. There was no statistical difference between

responders and non-responders regarding age, BMI, initial CDI-2/HDRS, treatment time, type of SSRI chosen, and additional sedative use. As expected, responders had significantly lower levels of HDRS and CDI-2 at t1 when compared with non-responders.

Table 3. Studied group characteristics.

	Whole Group (t0) n = 30	**Responders t(1) n = 13**	**Non-responders t(1) n = 17**	**Responders vs Non-responders**
Age [years]	13.07 (±1.26)	12.85 (±0.99)	13.24 (±1.44)	p = 0.4105
Sex	females	females	females	–
BMI [kg/m²]	20.89 (±3.47)	21.51 (±2.44)	20.41 (±4.10)	p = 0.1487
HDRS				
• t(0)	20 [13–30]	20 [14–30]	20 [13–28]	p=0.4445
• t(1)	8.5 [1–24]	4 [1–9]	12 [8–24]	p<0.0001*
CDI-2				
• t(0)	74.5 [60–79]	74 [66–79]	75 [60–79]	p = 0.9830
• t(1)	68 [47–79]	54 [47–68]	74 [60–79]	p < 0.0001*
Time of treatment [weeks]	7.27 (±1.41)	7.46 (±1.39)	7.12 (±1.45)	p = 0.5125
SSRI type				p = 0.6377
• Fluoxetine [n]	13	5	8	–
• Sertraline [n]	17	8	9	–
Additional sedative [n]	17	6	11	p = 0.3095
BDNF promoter MI [%]				
• t(0)	0.21 (±0.06)	0.23 (±0.08)	0.20 (±0.05)	p = 0.3900
• t(1)	0.22 (±0.07)	0.22 (±0.06)	0.21 (±0.07)	p = 0.6293

Continuous variables are presented as the mean and standard deviation; ordinal variables are presented as the median and range, t0 – on admission to the hospital before treatment, t1 – after minimum six weeks of antidepressant therapy, BMI – body mass index, HDRS – Hamilton Depression Rating Scale, CDI-2 – Children's Depression Inventory, BDNF – brain-derived neurotrophic factor, MI – methylation index, SSRI – selective serotonin reuptake inhibitor, * – statistically significant.

Molecular results

The analysis did not demonstrate any significant changes in MI between t0 and t1 in the whole studied group. No significant differences in MI were observed after stratifying the group according to the SSRI chosen (Figure 1a). Regardless of whether the patients clinically responded to treatment, there were no significant shifts in MI (Figure 1b).

Responders and non-responders did not differ regarding initial/final MI within BDNF exon IV promoter at t0 and t1 (Table 3). The univariate logistic regression analysis revealed no significant association between initial MI and remission status at t1 (Table 4). There were no visible associations between age, BMI, time of treatment, initial level of depressive symptoms, and treatment outcome (Table 4).

Discussion

We found no significant difference between the pre- and post-treatment methylation index in the BDNF gene exon IV promoter and no correlation between initial methylation and the antidepressant treatment outcome in our studied group of adolescents treated for the first-lifetime depressive episode. According to the research performed on adults by Tadić *et al.* (2014), hypomethylation in the BDNF gene was a predictor of worse response to antidepressant treatment regardless of antidepressant class. Still, similarly to our results, methylation levels did not change significantly following the 6-week therapy (Tadić *et al.*, 2014). On the other hand, Chen *et al.* (2011) reported an increase in BDNF exon IV promoter methylation during treatment while also confirming the predictive

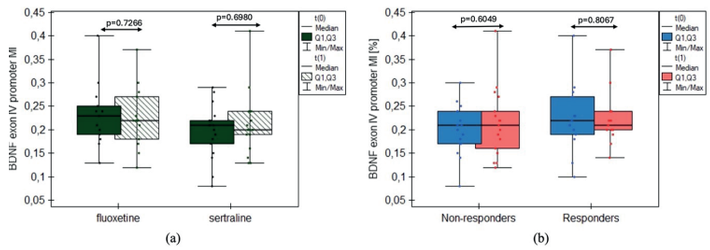

Figure 1. The results of the Wilcoxon test of the BDNF gene exon IV promoter Methylation Index (MI) before (t0) and after (t1) the treatment in the studied group stratified according to the type of SSRI (a) and treatment response (b)

Table 4. Results of the association between analyzed variables and positive treatment outcome in univariate logistic regression models for the whole sample.

Analyzed variable	b	95% CI	p-value
Age	−0.0101	−0.0621–0.0420	0.7035
BMI	0.1790	−0.3484–0.7064	0.5060
Time of treatment	0.0276	−0.0475–0.1027	0.4711
CDI (t0)	0.0112	−0.1552–0.1777	0.8948
HDRS (t0)	−0.0313	−0.2145–0.1518	0.7371
BDNF MI (t0)	6.5499	−5.9334–19.0332	0.3038

value between the level of the methylation and the occurrence of remission (Chen, Ernst and Turecki, 2011). Similar conclusions were reached by Lopez *et al.* (2013) and Wang *et al.* (2018), who in their prospective studies analyzing eight weeks of SSRI therapy, noticed an increase in responders' methylation results (Wang *et al.*, 2018) (Lopez *et al.*, 2013). Therefore, our results do not reflect the outcomes obtained in most of the studies performed on the adult population. Attempts to explain the above discrepancies should be sought in many aspects.

BDNF, as a factor directly related to neurogenesis, is an essential element in the development of the nervous system. Therefore, its gene expression might differ in the developmental population (Lee *et al.*, 2022) (Rodríguez-Carrillo *et al.*, 2023). It has been proven that its level in the blood decreases with age, which may be associated with increased neurodegeneration processes (Erickson *et al.*, 2010) (Molinari *et al.*, 2020) (Ted Kheng Siang Ng *et al.*, 2019). These processes have also been observed in adults with MDD (Webb *et al.*, 2020) (Bakusic *et al.*, 2021). BDNF values are more challenging to interpret in children and adolescents due to the physiologically increased secretion of this neurotrophin in the natural process of nervous system development, typical for this age group. A significant increase in peripheral BDNF and a decrease in methylation of the BDNF gene are observed particularly in early adolescence (Dincheva, Lynch and Lee, 2016) (Miguez *et al.*, 2020) (Zwolińska *et al.*, 2024).

Another aspect that may explain the lack of differences in MI before and after the treatment is the course of the disease among adolescents, which is known to differ from the presentation of the symptoms observed in adults. For instance, anhedonia and concentration disorders in MDD are more specific to older patients, while vegetative symptoms (appetite and weight change, loss of energy, and insomnia) are typical among youth (Rice *et al.*, 2019). Moreover, early depression is often characterized by acts of self-aggression, irritability or rebellious attitude (Gijzen *et al.*, 2021) (Richard G. Wight *et al.*, 2004)

(Tatsiopoulou *et al.,* 2020). It might be possible that different manifestations of symptoms in child depression result from different neurobiological underpinnings when compared with adults.

Remarkably, MDD among youth is significantly influenced by environmental factors (Stefanie Nelemans *et al.,* 2021). Yet, the number of studies in the adolescent population investigating epigenetic changes occurring as a response to environmental stressors is limited (Ochi and Dwivedi, 2023). Animal models have proven that severe stress in the early stages of life is associated with an increase in peripheral BDNF and the occurrence of epigenetic changes in its gene (Suri *et al.,* 2013). Interestingly, in the study performed on adults by Unternaehrer *et al.* (2015), there was a significant association between the history of low maternal care in childhood and greater DNA methylation in the BDNF gene (Unternaehrer *et al.,* 2015).

For the present research, the predictive value of the methylation level as a prognostic indicator of treatment response was not proven. In this context, it is worth considering the research of Lieb *et al.* (2018), which showed a correlation between the occurrence of remission in adults with MDD and the hypermethylation in the specific region of exon IV of the BDNF gene. However, that correlation characterized specifically the group of patients who suffered from severe depression before the treatment (Lieb *et al.,* 2018). It is assumed that younger patients are also more likely to respond to therapy when they present with severe depressive symptoms. Still, the relationship with epigenetic changes in the BDNF gene in this group of patients remains unknown (Kirsch *et al.,* 2008). Our study found no significant correlation between initial depressive symptoms severity and the treatment outcome.

Although the results of our work require an extended analysis, possibly on larger groups of patients, they demonstrate the importance of addressing depression in adults and youth separately. Further prospective studies should be designed to evaluate the association between antidepressant treatment and BDNF methylation status in order to expand our knowledge of depression pathophysiology across the lifespan and develop personalized treatment strategies. Further attempts to understand the relationship between epigenetic changes and MDD remission should combine molecular and clinical markers.

When interpreting the results of the foregoing study, certain limitations should be considered. Firstly, our research had a moderate study group size, which may have resulted in the insufficient statistical power for some tests. Therefore, potential statistical errors should be taken into account due to unsatisfactory analytical sensitivity. Secondly, the study group was limited to female patients, which may be considered both an advantage and disadvantage since the research on BDNF suggests sex-specific differences in BDNF gene expression, particularly during puberty (Ochi and Dwivedi, 2023) (Bath, Schilit and Lee, 2013) (Carbone and Handa, 2013).

Furthermore, we did not analyze the history of trauma, while studies emphasize a significant relationship between BDNF gene methylation and environmental stress (Ochi and Dwivedi, 2023) (Jo Wrigglesworth *et al.,* 2019). Another factors that could considerably impact our results include the family history of the disease, perinatal and intergenerational factors (Braithwaite *et al.,* 2015) (Provenzi *et al.,* 2022) (Labaut *et al.,* 2024). Moreover, certain environmental factors, such as diet or exposure to pollution, constitute significant limitations in methylation research (Kageyama *et al.,* 2022) (Rodríguez-Carrillo *et al.,* 2022) (Vicente Mustieles *et al.,* 2022).

Although the results of our work require an extended analysis, possibly on larger groups of patients, they demonstrate the importance of addressing depression in adults and youth separately. Further prospective studies should be designed to evaluate the association between antidepressant treatment and BDNF methylation status in order to expand our knowledge of depression pathophysiology

across the lifespan and develop personalized treatment strategies. Further attempts to understand the relationship between epigenetic changes and MDD remission should combine molecular and clinical markers.

Conclusions

We found no significant difference between the pre- and post-treatment methylation index in the BDNF gene exon IV promoter and no correlation between initial methylation and the antidepressant treatment outcome in our studied group of adolescents treated for the first-lifetime depressive episode. Continuation of research on larger study groups seems essential to verify the dynamics of epigenetic changes in the BDNF gene during antidepressant treatment in adolescence.

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REVIEW ARTICLE

MICROBES AND THE DEVELOPMENT OF DEMENTIA

MIKROORGANIZMY A ROZWÓJ OTĘPIENIA

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ABSTRACT

Introduction

Dementia represents one of the greatest challenges of modern medicine related to the ageing of the global population. The growing number of elderly people is contributing to an increase in the number of patients with dementing diseases, creating significant public health implications. The pathogenesis of diseases such as Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) or vascular dementia (VaD) is not fully understood. Recent theories suggest a possible involvement of microorganisms in the development of dementia.

Aim

The aim of this review is to assess the current knowledge of the likely contribution of microorganisms to the manifestation of dementia and their potential role as diagnostic and prognostic factors in the future.

Material and methods

Our review involved freely accessible databases: PubMed, Google Scholar, ScienceDirect, using keywords such as: dementia, microbes, virulent factors, neuroinflammation, neurodegenerative disorders.

Results

This review highlights the likely relationship between microorganisms such as Porphyromonas gingivalis and Helicobacter pylori and the development of dementing diseases such as Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies and vascular dementia.

Conclusions

Microorganisms including Porphyromonas gingivalis and Helicobacter pylori and their virulent factors are most likely to be involved in the pathogenesis of dementia diseases. Among these are lipopolysaccharide (LPS), gingipains and cytotoxin-associated protein A (CagA).

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STRESZCZENIE

Wstęp

Otępienie stanowi jedno z największych wyzwań współczesnej medycyny związanych ze starzeniem się populacji ogólnoświatowej. Rosnąca ilość osób starszych przyczynia się do zwiększenia ilości pacjentów z chorobami otępiennymi, co stwarza istotne implikacje dla zdrowia publicznego. Patogeneza chorób takich jak choroba Alzheimera (AD), otępienie czołowo-skroniowe (FTD), otępienie z ciałami Lewy'ego (DLB) czy otępienie nacznyniowe (VaD) nie jest do końca poznana. Najnowsze teorie sugerują możliwy udział mikroorganizmów w powstawaniu otępienia w tych chorobach.

Cel

Celem niniejszego przeglądu jest ocena aktualnej wiedzy na temat prawdopodobnego udziału mikroorganizmów w ujawnieniu się otępienia oraz ich potencjalnej roli jako czynników diagnostycznych i prognostycznych w przyszłości.

Materiał i metody

Nasz przegląd obejmował ogólnodostępne bazy danych: PubMed, Google Scholar, ScienceDirect, przy użyciu słów kluczowych takich jak: otępienie, mikroorganizmy, czynniki wirulentne, neurozapalenie, choroby neurodegeneracyjne.

Wyniki

W niniejszym przeglądzie zwrócono uwagę na prawdopodobną zależność między mikroorganizmami takimi jak Porphyromonas gingivalis i Helicobacter pylori a rozwojem chorób otępiennych takich jak: choroba Alzheimera, otępienie czołowo-skroniowego, otępienie z ciałami Lewy'ego i otępienie naczyniowe.

Wnioski

Mikroorganizmy m.in. Porphyromonas gingivalis i Helicobacter pylori oraz ich czynniki wirulentne najprawdopodobniej uczestniczą w patogenezie chorób otępiennych. Wśród nich wymienia się: lipopolisacharyd (LPS), gingipainy oraz białko A związane z cytotoksyną (CagA).

Słowa kluczowe: porphyropmonas gingivalis, helicobacter pylori, czynniki wirulentne, choroby neurodegeneracyjne

Introduction

Dementia is a significant public health challenge and an escalating burden due to the aging global population. It is a syndrome characterized by progressive impairment of cognitive functions, including memory, reasoning, and executive abilities. Rather than a single disease, dementia is best understood as a syndrome encompassing several subtypes, including Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and vascular dementia (VaD) (Guerreiro *et al.* 2020). The etiology of dementia is multifactorial, involving primary neurological, neuropsychiatric, and systemic medical conditions. It is frequently the case that multiple underlying pathologies converge in a single patient to produce the clinical manifestations of dementia (Błaszczyk

2022). In earlier years, research on dementia has focused on genetic predispositions – such as mutations in the APP, PSEN1, and PSEN2 genes, and on pathophysiological mechanisms, including the deposition of beta-amyloid plaques (Aβ) and tau protein aggregates in the brain (Van Cauwenberghe *et al.* 2016). However, a growing body of evidence highlights the critical role of microorganisms, both pathogenic and symbiotic, in the initiation and progression of neurodegenerative processes. Recent studies have increasingly emphasized the gut-brain axis (GBA), which underscores the multidimensional interplay between the gut microbiota and the central nervous system (CNS) (Seo and Holtzman 2024). The gut microbial communities play essential roles in maintaining physiological homeostasis and regulating metabolic processes, including immune system development, nutrient absorption, and vitamin synthesis (Bain and Cerovic 2020). Emerging evidence indicates that alterations in the gut microbiota, known as dysbiosis, are associated with dementia (Stadlbauer *et al.* 2020). Dysbiosis has been linked to chronic systemic inflammation, which may influence the brain via several mechanisms, including the release of proinflammatory cytokines (e.g. interleukin 6 (IL-6), tumor necrosis factor (TNF-α)), bacterial metabolites, and neural pathways such as the vagus nerve (Figure 1) (Anand *et al.* 2022). Furthermore, studies investigating bacterial pathogens Porphyromonas gingivalis have suggested their involvement in the pathogenesis of neurodegenerative diseases such as AD (Zhao *et al.* 2024).

The aim of this review is to analyze and synthesize current evidence regarding the role of microorganisms in the pathogenesis of dementia. Considering microorganisms as factors involved in the development of dementia opens new research opportunities and potential therapeutic pathways that could reduce the burden of neurodegenerative diseases in aging societies.

Clinical features of dementia

Dementia is characterized by an acquired, chronic loss of cognitive function caused by brain injury or disease, contributing to progressive impairments in thinking, memory, and behavior, often combined with emotional and language difficulties, hindering occupational or social function (Arvanitakis *et al.* 2019). According to the currently valid fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5), the diagnosis of dementia, defined as major neurocognitive disorder (MND), requires substantial impairment in at least one cognitive domain. The cognitive domains include complex attention, social cognition, language, learning and memory, perceptual-motor/visuospatial function, and executive functioning. Furthermore, to diagnose dementia, the clinician needs to ensure that it cannot be better explained by another mental disorder and that the cognitive impairment does not present exclusively in the context of delirium. Another important factor is the determination of the underlying etiology. On the other hand, a diagnosis of mild cognitive impairment (MCI) is established when there is modest impairment in at least one cognitive domain. In contrast to patients with dementia, individuals affected by MCI are still able to perform everyday activities individually but with great difficulties (Emmady *et al.* 2024).

Studies have demonstrated that healthcare professionals do not diagnose dementia or cognitive impairment properly enough. On the other hand, screening cognitive tests are useful tools to assess patients' cognitive status. One of the most commonly used is the Mini-Mental State Examination (MMSE), however, there are also other tests available: Montreal Cognitive Assessment (MoCA), ACE-R, Abbreviated Mental Test, Clock Drawing Tests, GPCOG, IQCODE, Mini-Cog test, Memory Impairment Screen, verbal fluency test, and others (Tsoi *et al.* 2015). Recent developments in nuclear medicine have provided other possibilities for dementia diagnosis. Positron emission tomography

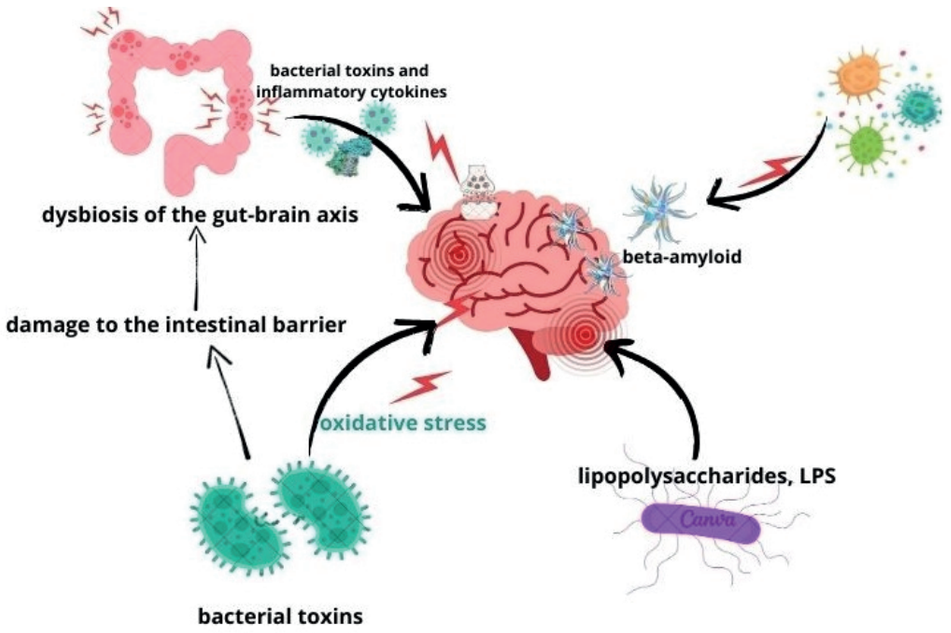

Figure 1. Mechanisms linking microorganisms with dementia. Illustration of the mechanisms linking mie croorganisms with dementia. It presents processes such as dysbiosis of the intestinal microbiota, damage to the gut-brain barrier, direct infections, neuroinflammation and the formation of beta-amyloid deposits.

(PET) plays an important role in the early and specific diagnosis of dementia, contributing to suitable medical management and clinical prognostication (Burkett *et al.* 2022). Since dementia is characterized by neuronal cell loss, currently, there is no curative treatment for this disorder. Nevertheless, therapeutic interventions are used to alleviate the behavioral and cognitive consequences of dementia (Hafiz *et al.* 2023). Indeed, patients affected by dementia often suffer from neuropsychiatric symptoms, which include depression, apathy, aggression, anxiety, irritability, sleep disorders, aberrant motor behaviors, delusions, and others (Radue *et al.* 2019). A 2024 Lancet Commission report provided recommendations for people with dementia stating that neuropsychiatric symptoms should be treated using activity and care-coordinated multicomponent interventions (Livingston *et al.* 2024). Moreover, patients suffering from AD or DLB should use cholinesterase inhibitors and memantine. Interestingly, the Commission determined fourteen risk factors for developing dementia and proposed various actions to reduce dementia risk, such as cognitively stimulating activities, education, hypertension prevention, depression treatment, reduction of air pollution, alcohol consumption, and cigarette smoking. These actions might be promoted by healthcare professionals, contributing to a decrease in dementia prevalence.

Dementia biomarkers

In the early stages of dementia, symptoms may be subtle and inconspicuous, often not becoming apparent until they begin to significantly impair the patient's quality of life. Initially, these symptoms can be misattributed to normal aging processes, thereby delaying the recognition and diagnosis of the condition. As a result, the early diagnosis of dementia remains a major challenge in the field of neurology. For this reason, the identification of reliable diagnostic and prognostic biomarkers has been a focal point of research worldwide for many years.

One of the leading theories of AD pathogenesis suggests that the aggregation of Aβ plays a central role in the development of the disorder. As a result, Aβ has been extensively studied as a potential biomarker in brain imaging, cerebrospinal fluid (CSF) and blood

analysis. PET imaging enables the quantification and localization of Aβ deposits in the brain through the selective binding of the Pittsburgh Compound-B (PiB) ligand. The Aβ40/ Aβ42 ratio in CSF can serve as a valuable diagnostic tool, as it is a highly effective predictor of amyloid positivity in PET imaging. However, there is high costs and invasiveness associated with imaging and CSF analysis. Recent studies have demonstrated that the ratio of plasma APP669-711/Aβ1-42 and Aβ1-40/Aβ1-42 can effectively reflect beta-amyloid burden in the brain (Nakamura *et al.* 2018). Another critical biomarker of AD is neurofibrillary tangles (NFTs), which are composed of hyperphosphorylated tau (p-tau) protein. These intracellular aggregates disrupt microtubule stability, compromise axonal transport, and contribute to neuronal dysfunction and degeneration. P-tau is a relatively specific biomarker for AD, as its concentration in CSF correlates with the extent of NFTs pathology. However, elevations in total tau levels in CSF may reflect not only NFT accumulation but also neuronal and synaptic damage, which occurs in various neurodegenerative disorders as well as in traumatic brain injuries.

FTD is a heterogeneous disorder with different clinical phenotypes, considering the behavioural form (bvFTD) and primary progressive aphasia (PPA). Due to the aggregation of specific proteins, FTD can be divided into: FTLD-TDP (frontotemporal lobar degeneration associated with TDP-43) , FTLD-TAU (frontotemporal lobar degeneration associated with TAU protein) and FTLD-FUS (frontotemporal lobar degeneration associated with FUS protein). The most common subtype of FTD is FTDL-TDP. The pathogenesis of FTLD-TDP is characterized by the accumulation of hyperphosphorylated and ubiquitinated TDP-43, which forms toxic, insoluble aggregates. TDP-43 aggregates in the brain are characteristic of FTLD-TDP, however, the use of TDP-43 as a biomarker is challenging, as it predominantly aggregates in neurons and is not always released in significant amounts into the CSF and blood (Katisko *et al.* 2022). The potential marker for all subtypes of FTD is neurofilament light chain (NfL), which is released into the extracellular space as a result of neuronal damage, from where it can enter both the CSF and bloodstream. Serum levels of NfL have consistently been found to be elevated in patients with FTD with higher levels in patients with FTLD-TDP than with FTLD-TAU. (Abu-Rumeileh *et al.* 2018, Weintraub *et al.* 2021). Furthermore, NfL levels also correlate with disease severity, with higher concentrations reflecting a more advanced clinical phenotype. An additional advantage of NfL as a biomarker is its ability to detect the disease up to 15 years prior to the onset of clinical symptoms (Gifford *et al.* 2023).

The pathogenesis of DLB is primarily driven by the pathological aggregation of α-synuclein which forms insoluble structures known as Lewy bodies, suggesting that α-synuclein could have potential as a biomarker for the disease. However, while total α-synuclein levels in CSF are typically reduced in patients with DLB, these levels can overlap with those observed in control groups and individuals with other neurodegenerative conditions, which reduces the specificity of α-synuclein as a definitive diagnostic marker for DLB (Hanson 2021). Nevertheless, recent studies have shown that oligomeric α-synuclein, when measured in combination with tau protein, holds more promise as a specific biomarker in differentiating DLB from AD (van Steenoven *et al.* 2018).

In case of VaD, its pathogenesis has been linked to malabsorption of cobalamin leading to elevated levels of homocysteine (Hcy), an amino acid whose excessive accumulation contributes to vascular endothelial dysfunction and increased cerebrovascular risk. Hyperhomocysteinemia has been implicated in promoting atherosclerosis, oxidative stress, and neuroinflammation, all of which may exacerbate cerebrovascular pathology and cognitive decline (Nillson *et al.* 2013). Furthermore, clinical studies suggest that elevated Hcy levels are associated with an

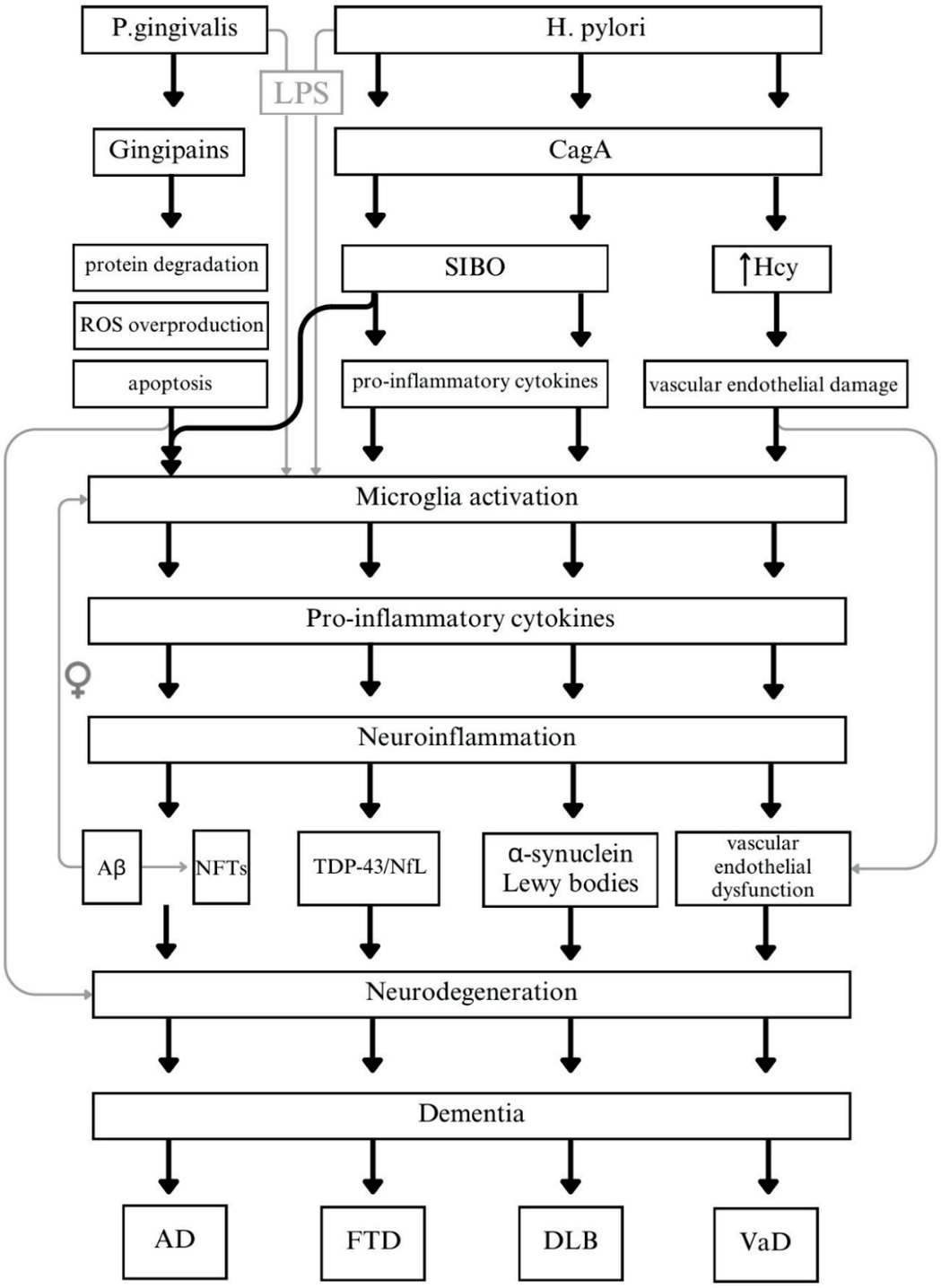

Figure 2. Detailed mechanisms linking microorganisms with AD, FTD, DLV and VaD. LPS – lipopolysaccharide, CagA – cytotoxin-associated protein A, SIBO – small intestinal bacterial overgrowth, ROS – reactive oxygen species, Hcy – homocysteine, Aβ - beta-amyloid plaques, NFTs – neurofibrillary tangles, TDP-43 – TAR DNA-binding protein 43, NfL – neurofilament light chain, AD - Alzheimer's disease, FTD – frontotemporal dementia, DLB – dementia with Lewy bodies, VaD – vascular dementia.

increased risk of progression from MCI to dementia (Zuliani *et al.* 2024).

Emerging research also highlights the potential role of infectious markers in the pathogenesis and progression of various neurodegenerative diseases. Evidence suggests that microbial infections, viral pathogens, and associated inflammatory responses may contribute to neurodegenerative processes by triggering immune activation, promoting protein misfolding, and exacerbating neuronal damage.

Virulent factors and the development of dementia

Virulence factors are molecules produced by pathogenic microorganisms that are crucial for the initiation and progression of many diseases. They include toxins, adhesins, and other molecules that facilitate attachment to, invasion of, and evasion of host immune defenses. These factors allow pathogens to colonize host tissues, overcome the natural resistance of the microbiome, and adapt the host environment to their advantage (Petersson *et al.* 2023). These molecules are not only critical for the pathogenicity of microorganisms but also represent potential targets for therapeutic interventions. Understanding their mechanisms is crucial for developing innovative strategies to combat infectious diseases and address challenges like antimicrobial resistance. Virulence factors have been implicated in mechanisms such as chronic inflammation, disruption of neuronal homeostasis, and amyloid pathology. The complement system, a critical component of innate immunity, becomes overactivated in response to certain bacterial and viral virulence factors, which leads to neuronal damage and synaptic loss. Pathogens expressing adhesins and other virulence factors can compromise blood-brain barrier (BBB), facilitating their entry into the CNS. Certain microbial virulence factors stimulate the production and aggregation of Aβ, a key pathological hallmark of AD. This process activates the complement system and promotes glial cell-mediated inflammation, further damaging neuronal networks. Microglia, the brain's immune cells, are activated in response to microbial virulence factors. While acute activation is protective, chronic stimulation leads to sustained neuroinflammation and neuronal injury. Persistent infections or continuous exposure to virulence factors exacerbate this microglial overactivation, creating a feedback loop that accelerates neurodegeneration (Shinjyo *et al.* 2021).

Virulence factors represent a significant but underexplored contributor to dementia pathogenesis. Through chronic neuroinflammation, BBB disruption and Aβ aggregation, these microbial components exacerbate neurodegenerative processes. Future research should focus on elucidating these interactions and developing targeted interventions to address this critical aspect of dementia etiology.

Porphyromonas gingivalis, can it cause the development of dementia?

Porphyromonas gingivalis is a gram-negative anaerobic bacterium that is one of the bacterial species that causes periodontitis (Verma *et al.* 2023). This disease is manifested by gingival swelling, vascular congestion, redness, the formation of periodontal pockets, and the progressive destruction of the bone and soft tissues that support the teeth (Fu *et al.* 2023). Periodontal disease is associated with various other disorders including rheumatoid arthritis, cardiovascular disease, type II diabetes and cognitive disorders such as early, middle and/or late dementia and AD (Nara *et al.,* 2021). Emerging evidence indicates a correlation between chronic periodontitis and dementia or sporadic AD (Shinjyo and Kita 2021; Verma *et al.* 2023).

Periodontal bacteria or bacterial particles can enter the brain through the bloodstream or peripheral nerves (Fu *et al.* 2023). Outer membrane vesicles (OMVs) carry various bacteria factors, such as gingipains and LPS, facilitating their delivery to various tissues within the host organism. Gingipains play

a pivotal role in neuronal degeneration by both indirectly activating microglia, thereby inducing chronic neuroinflammation, and directly damaging neurons through the overproduction of reactive oxygen species (ROS), protein degradation, and the promotion of apoptosis (Nara *et al.* 2021). The brain tissue of patients with AD showed higher levels of gingipains than non-AD subjects. A positive correlation was also found between the presence of gingipains and tau load as well as ubiquitin load (Dominy *et al.,* 2019). LPS stimulates cells to produce pro-inflammatory cytokines and its presence has been detected in the postmortem brains of AD patients, whereas it was not found in the brains of non-AD subjects (Poole *et al.* 2013; Verma *et al.* 2023). By activating microglia, LPS facilitates the formation of Aβ, the presence of which triggers a pathophysiological cascade that culminates in the hyperphosphorylation of tau and the accumulation of NFTs (Fu *et al.* 2023). P. gingivalis and its virulence factors not only promote the production of proinflammatory molecules, such as IL-1β, IL-6 and TNF-α, but also decrease the expression of anti-inflammatory mediators including IL-10 and IL-4. Higher level of pro-inflammatory cytokines lead to an increased level of inflammatory mediators in the brain, which directly contributes to neurodegeneration. Therefore, P. gingivalis and its virulence factor may have an impact on the development of dementia.

Helicobacter pylori and dementia development

Helicobacter pylori is a gram-negative bacterium, commonly found in a human stomach after being infected usually during childhood. There are two ways for H. pylori infection to occur – through ingestion or transmission from mother to fetus during pregnancy (Erickson *et al.* 2023). Frequently it causes chronic gastritis leading to pathological conditions such as gastric cancer, peptic ulcer disease or MALT lymphoma. Half of the world human population is infected with H. pylori (Malfertheiner *et al.* 2023). There are many pathogens associated with increased risk of developing dementia and H. Pylori is one of them (Roubaud Baudron *et al.* 2013). H. pylori infection pathomechanism is based on inducing production of interleukins, c-reactive protein (CRP), and TNF-α which promote neuroinflammatory response (Piekut *et al.* 2022). In vitro studies about H. Pylori infection influence were carried out with use of mouse neuroblastoma N2a cells – it turned out that infected cells contributed to increasing hyperphosphorylation of tau protein, which is one of the dementia and AD causes. Those cells produce enhanced amount of presenilin 2 and Aβ42 and above that they activated glycogen synthase kinase-3β (Wang *et al.* 2015).

Another important mechanism in H. pylori infection leading to dementia involve bacteria OMVs, which are important in virulence as they let bacteria release toxins and enzymes to the host. Studies were carried out on Rosa26. tdTomato mouse model using Crerecombinase-labelled OMVs, that enabled detecting the OMVs distribution in a mouse body. This study has shown that OMVs reach not only stomach, but also kidneys, liver and brain. Cells with positive signal were found in brain cortex and hippocampus (Xie *et al.* 2023). This study also has shown increased amount of Aβ in OMVs-treated AppNL-G-F mice brain (mostly in CA1, CA2 and CA3 regions), which is typical for AD.

Those were some mechanisms that were found out in studies on how H. pylori infection may influence dementia development. There are also studies on humans that show H. pylori infection could affect cognitive functioning. Erickson *et al.* (2023) found out there is possible association between H. pylori seropositivity and dementia development as there were statistically significant results for H. pylori positive patients with worse results on the Reasoning task, which is used to measure cognitive functioning. There were also studies on correlation between H. pylori infection and Alzheimer disease. Douros *et al.* (2024) found in their study that the risk of AD after being infected with H. pylori was

increased on 11% in patients at age 50 years old or more. After a decade since H. pylori infection onset occurred, the risk of developing AD surged to 24%. There are few possible explanations for link between these two conditions. H. Pylori infection can induce intestinal dysbiosis, particularly small intestinal bacterial overgrowth (SIBO), which disrupts the gut-brain axis. This dysbiosis promotes the production of pro-inflammatory cytokines and activates pathological pathways that contribute to the development of neurodegenerative disorders, including dementia. Cobalamin malabsorption is commonly associated with H. Pylori infection, resulting in elevated Hcy levels that contribute to vascular endothelial damage. This endothelial dysfunction subsequently triggers microglial activation, which, through the release of pro-inflammatory cytokines, promotes chronic neuroinflammation. Furthermore, damage to the vascular endothelium disrupts normal blood flow and impairs oxygen delivery to neurons, leading to neuronal hypoxia, subsequent neuronal cell death and eventually to VaD. (Cárdenas *et al.* 2019).

Conclusion

The existing literature indicates a significant correlation between microbial infections and the pathogenesis of dementia, with particular emphasis on Porphyromonas gingivalis and Helicobacter pylori. Key mechanisms implicated in this process include chronic inflammation, protein degradation, and disruption of the BBB, all of which may contribute to disease progression. Consequently, the virulence factors of these microorganisms hold potential as biomarkers for the early detection and monitoring of dementia. Further research is required to elucidate the precise impact of these infections on neurodegeneration and to identify effective therapeutic strategies for affected patients.

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Acknowledgments

Under acknowledgments please specify contributors to the article other than the authors accredited. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proofreading the article, etc.). Also, acknowledge all sources of support (grants from government agencies, private foundations, etc.). The names of funding organizations should be written in full.

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Rang, H. P., Dale, M. M., Ritter, J. M., Moore, P. K. Pharmacology. 5th Ed. Edinburgh: **Churchill Livingstone**; 2003, Phillips, S. J., Whisnant, J. P. *Hypertension and stroke. In: Laragh JH, Brenner BM, Editors. Hypertension: pathophysiology, diagnosis, and management.* 2nd Ed. New York: Raven Press; 1995. pp. 465–478.

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Książki:

Rang, H. P., Dale, M. M., Ritter, J. M., Moore, P. K. Pharmacology. 5th Ed. Edinburgh: **Churchill Livingstone**; 2003, Phillips, S. J., Whisnant, J. P. *Hypertension and stroke. In: Laragh JH, Brenner BM, Editors. Hypertension: pathophysiology, diagnosis, and management.* 2nd Ed. New York: Raven Press; 1995. s. 465–478.

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