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COINCIDENCE OR BIOLOGICAL LINK? HEREDITARY HEMOCHROMATOSIS AS A POTENTIAL RISK FACTOR FOR MULTIPLE SCLEROSIS

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ABSTRACT

Disorders of Iron metabolism may play an important role in the pathogenesis of multiple sclerosis (MS), alongside others, by increasing oxidative stress, inflammatory processes or the damage of oligodendrocytes. Excessive iron accumulation, observed in congenital hemochromatosis , might promote demyelinating processes which suggests a potential biological link between these conditions. This theme presents the case of a 41-year-old man, who's diagnosed with congenital hemochromatosis associated with a mutation in the HFE gene and demyelinating lesions that suggests multiple sclerosis which follows extensive diagnostic testing, performed as part of preventing set of tests. Laboratory tests revealed significantly elevated levels of iron and ferritin, also brain MRI shown multiple demyelinating lesions typical for MS. Genetic testing confirmed a homozygous c.845G>A mutation in the HFE gene. Immunomodulating treatment with oftamumab and phlebotomy were implemented, resulting in improvement of iron metabolism parameters. This described case may indicate the potential involvement of iron homeostasis disorders in the pathogenesis demyelinating processes, but cause effect bond remains ambiguous. Further studies are required to assess the iron overload role in the development and course of multiple sclerosis and the potential importance of hemochromatosis as a disease-modifying factor.

KEYWORDS

Multiple Sclerosis; Hereditary Hemochromatosis; Iron Metabolism; Oxidative Stress; Ferroptosis; HFE Mutation

CITATION

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Introduction

Dysregulation of iron metabolism in the brain plays a significant role in the aging process and the pathogenesis of multiple neurodegenerative diseases [1]. In hereditary hemochromatosis, HFE gene mutations lead to excessive iron absorption in the gastrointestinal track and its deposition in various organs, potentially including central nervous system [2]. Overabundance of iron can lead to the synthesis of reactive oxygen species, inflated oxidative stress, inflammation and induction of ferroptosis- a regulated form of iron-depended cell death [1,5].

Accumulating evidence suggests that disturbances in iron homeostasis may also play a role in pathogenesis of multiple sclerosis (MS). Magnetic Resonance Imaging (MRI) studies have shown an increased iron deposition inside deep brain structures in MS patients, particularly in the basal ganglia and thalamus [3,6]. The degree of iron accumulation might correlate with disease activity and the severity of neurological deficits [8].

Iron plays a vital role in central nervous system functioning by participating in neurotransmitter synthesis, myelin production and neuronal energy metabolism, among many processes. In recent years happened an increased analysis of the potential contribution of iron metabolism disorders to the development of demyelinating diseases, including multiple sclerosis [3,7].

Hereditary hemochromatosis is one of the most common genetic diseases in the European population. It is mostly associated with the C282Y mutation of the HFE gene, leading to increased iron absorption from the gastrointestinal tract and its pathological deposition in tissues [2]. Although hemochromatosis is traditionally mainly associated with liver, pancreas, and heart damage, a growing number of publications highlight the possible neurological consequences of chronic iron overload [9].

All data used in this study were collected and processed in full compliance with applicable ethical standards and regulations concerning the protection of personal data. The information presented in this work has been thoroughly anonymized, and no elements that could directly or indirectly identify the participant have been disclosed. Any potentially identifiable details have been modified or omitted to ensure complete confidentiality while preserving the scientific value of the data. Prior to inclusion in the study, the participant

was fully informed about the nature, purpose, and scope of the research, including the intention to use the collected data for scientific analysis and publication. The participant received clear and comprehensive information regarding how the data would be handled, stored, and presented in an anonymized form. Written informed consent was obtained from the participant before any data collection took place. The consent explicitly covered the use of anonymized clinical information for research purposes, as well as permission for publication, including the description of the case in a scientific context. The data was included in the patient's records. The participant confirmed their understanding of the study procedures and voluntarily agreed to participate, with the right to withdraw consent at any stage without any consequences. All procedures performed in this study were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant national guidelines, here is the quote that best conveys the essence of our work:„In medical research involving human participants capable of giving informed consent, each potential participant must be adequately informed in plain language of the aims, methods, anticipated benefits and potential risks and burdens, qualifications of the researcher, sources of funding, any potential conflicts of interest, provisions to protect privacy and confidentiality, incentives for participants, provisions for treating and/or compensating participants who are harmed as a consequence of participation, and any other relevant aspects of the research. The potential participant must be informed of the right to refuse to participate in the research or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information and communication needs of individual potential participants as well as to the methods used to deliver the information. After ensuring that the potential participant has understood the information, the physician or another qualified individual must then seek the potential participant's freely given informed consent, formally documented on paper or electronically. If the consent cannot be expressed on paper or electronically, the non-written consent must be formally witnessed and documented. All medical research participants should be given the option of being informed about the general outcome and results of the research."[10]

We present here an unusual case of coexistence of congenital hemochromatosis and demyelinating disease of the central nervous system, as well as to discuss potential biological mechanisms linking iron metabolism disorders with the pathogenesis of multiple sclerosis.

Methodology

This work was written in a way of case report of a patient diagnosed and treated for a concomitant demyelinating disease of the central nervous system and hereditary hemochromatosis. The complete set of his medical record were reviewed, including the diagnostic procedures of inpatient and outpatient, laboratory, MRI, test results and data regarding patient's treatment and clinical follow up as well.

The clinical material included records of patient's hospitalizations between 2018 to 2025, also his specialist consultations regarding neurology and hematology, cerebrospinal fluid (CSF) tests, and genetic testing for HFE gene mutations. The main focus was shifted towards to the dynamics of neurological symptoms, the timing of subsequent relapses, and the possible relationship between symptom severity and iron metabolism parameters.

The laboratory analysis primarily rated parameters related to the iron metabolism, which includes serum iron concentration, ferritin, and basic blood count parameters. The results were interpreted in relation to current laboratory standards and current guidelines for the diagnosis of congenital hemochromatosis. Following the implementation of phlebotomy, changes in biochemical parameters were also analyzed. Imagine diagnostics were performed by MRI of the brain and cervical spinal cord. The images were assessed based on radiological descriptions and criteria specific to demyelinating diseases of the central nervous system. The location of demyelinating lesions, their morphology and distribution in time and space were considered, in accordance with current diagnostic criteria for multiple sclerosis. NMOSD spectrum disorders were also considered in other analysis.

Genetic testing was performed using molecular analysis of the HFE gene in a certified diagnostic laboratory. The presence of the most common mutations associated with hereditary hemochromatosis on the c.845G>A (p.Cys282Tyr) variant gene was discovered. These genetical test results were compared with the patient's symptoms and iron metabolism parameters. The clinical assessment considered how effective the immunomodulatory treatment with ofatumumab was, also theiron reduction therapy by the method regular bloodletting. How the impact of treatment on the patient's neurological status, the severity of subjective symptoms, and changes in laboratory levels (main focus of ferritin) was evaluated.

Furthermore the conduction of a narrative review about the current role of iron in the pathogenesis of multiple sclerosis and other neurodegenerative diseases, from current scientific literature, was included. The

investigation included publications on oxidative stress, ferroptosis, oligodendrocyte dysfunction, and the impact of HFE gene mutations on the functions of the central nervous system. The literature used in this work consisted of original articles, review papers, and reports on the use of current magnetic resonance imaging techniques in assessing the disposition of the iron brain.

The nature of this study is observational and descriptive, which limitations include incampacity of determination, whether there is a cause-and-effect relationship between iron overload and the development of multiple sclerosis. However, the obtained data might become a basis for further research on the potential impact of iron homeostasis disorders on demyelinating and neurodegenerative processes.

Case report

A 41-year-old patient first reported neurological symptoms in 2018. Symptoms consisted of chronic cervical spine pain and an episode of double vision, which involved two weeks. An MRI of the cervical spine, performed at that time, showed degenerative lesions in the cervical vertebrae. The symptoms were attributed to spinal pathology, and conservative treatment was initiated.

In May 2024, as part of the "Prophylaxis 40 PLUS" preventive program, the patient visited his primary care physician for a checkup. During this time, new neurological symptoms emerged, including voiding disorders. Patient reported a feeling of urgency and intermittent inability to urinate, despite repeated attempts for several minutes. Additionally, in the past few years, he had been experiencing nonspecific symptoms: chronic fatigue, dizziness, weakness and less sensitivity to cold

Basic laboratory tests were normal. However, as part of the extended diagnostic checkup- iron metabolism parameters were measured. An elevated iron concentration of 217 μg/dl (normal range: 33–193 μg/dl) and ferritin of 1062 ng/ml (normal range: 30–400 ng/ml) were detected. These results raised the suspicion of hemochromatosis.

Due to persistent neurological symptoms, an MRI of the brain and cervical spinal cord was performed. The MRI revealed numerous demyelinating lesions which suggested a demyelinating disease of the central nervous system. The differential diagnosis included multiple sclerosis and neuromyelitis optica spectrum disorder (NMOSD). The presence of juxtacortical lesions, known as Dawson's fingers, and the characteristic morphology of the lesions in the brain and cervical cord supported the diagnosis of MS. Furthermore, involvement of the area postrema and subependymal lesions within the corpus callosum could suggest NMOSD.

The patient was referred for further neurological and hematological evaluation. Neurological examination revealed lesions suggesting central nervous system damage. Additionally, deep abdominal muscle atrophy was observed, including the rectus abdominis, obliques, and transverse abdominis muscles. Cerebrospinal fluid analysis and in-depth diagnosis were performed.

Genetic diagnostics performed at the Genomed laboratory confirmed the presence of a homozygous HFE gene mutation c.845G>A (p.Cys282Tyr), which allowed the diagnosis of congenital hemochromatosis.

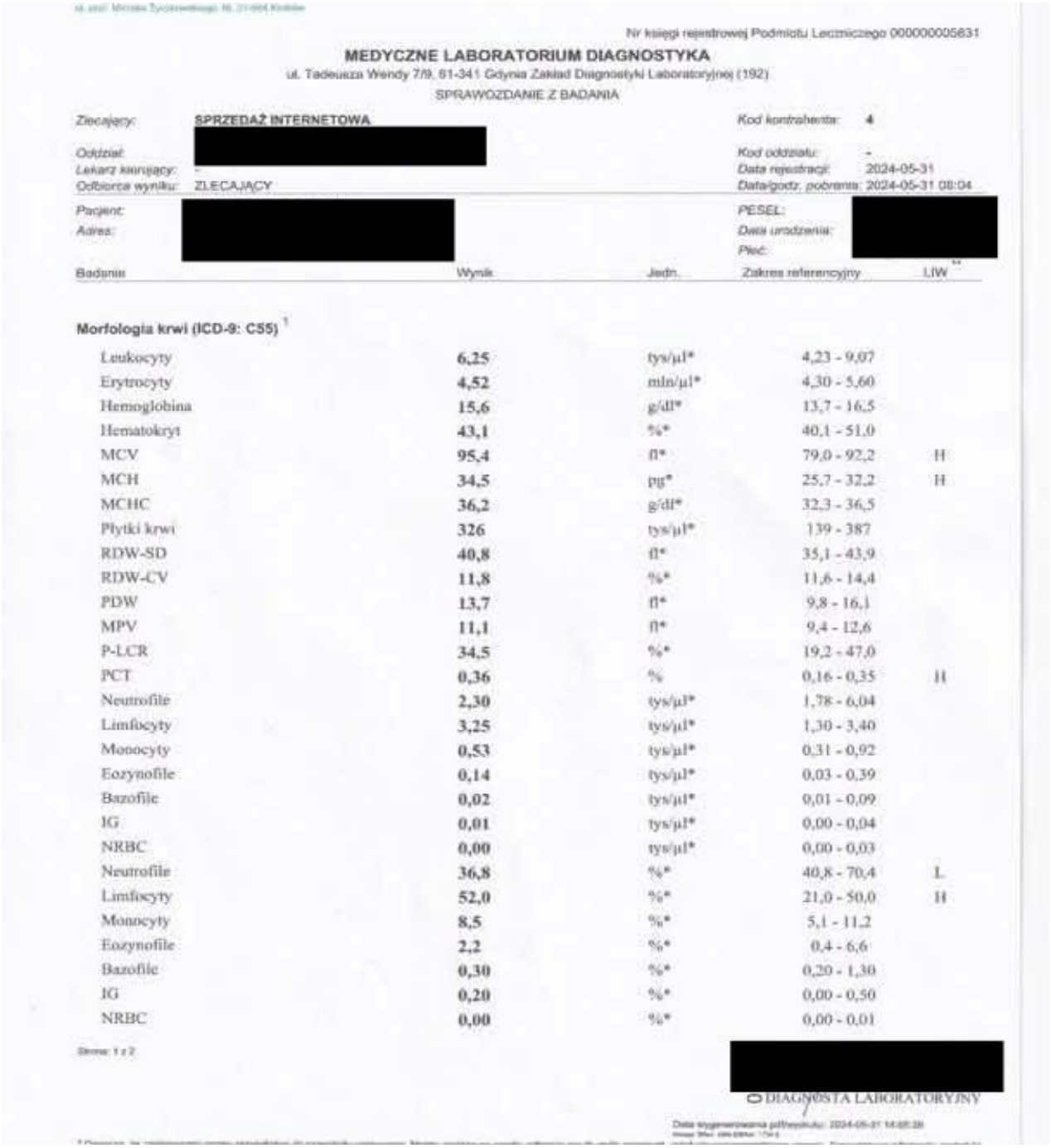
On January 18, 2025 immunomodulatory treatment with 20 milligrams of ofatumumab was initiated. In February 2025, patient’s neurological condition worsened, with the development of proprioceptive disturbances on the left side of his body. He was re-hospitalized and received intravenous glucocorticoid therapy (20 milligrams/day of Encortron) for five days.

Despite the occurring treatment, patient showed no improvement by continuing og having persistent proprioceptive disturbances, chronic fatigue, and frequent dizziness. He reported that similar symptoms have been occurring sporadically since his childhood.

Meanwhile a treatment for hemochromatosis was implemented with regular bloodletting, once every 3 months. After three treatments, significant improvement in iron metabolism was achieved—ferritin concentration decreased to 199 ng/ml and iron levels went down to 63 ug/dl.

The patient did not show any other characteristic symptoms of hemochromatosis such as hepatomegaly or arrhythmias resulting from myocardial hemosiderosis.

Results



Nr księgi rejestrowej Podmiotu Leczniczego 000000005631

MEDYCZNE LABORATORIUM DIAGNOSTYKA

ul. Tadeusza Wendy 7/9, 81-341 Gdynia Zakład Diagnostyki Laboratoryjnej (192)

SPRAWOZDANIE Z BADANIA

Zlecający: SPRZEDAŻ INTERNETOWA — Kod kontrahenta: 4

Oddział: [redacted] — Kod oddziału: -

Lekarz kierujący: - — Data rejestracji: 2024-05-31

Odbiorca wyniku: ZLECAJĄCY — Data/godz. pobrania: 2024-05-31 08:04

Pacjent: [redacted] — PESEL: [redacted]

Adres: — Data urodzenia:

Płeć:

Morfologia krwi (ICD-9: C55) [1]

Badanie	Wynik	Jedn.	Zakres referencyjny	LIW**
Leukocyty	6,25	tys/µl*	4,23 - 9,07	
Erytrocyty	4,52	mln/µl*	4,30 - 5,60	
Hemoglobina	15,6	g/dl*	13,7 - 16,5	
Hematokryt	43,1	%*	40,1 - 51,0	
MCV	95,4	fl*	79,0 - 92,2	H
MCH	34,5	pg*	25,7 - 32,2	H
MCHC	36,2	g/dl*	32,3 - 36,5	
Płytki krwi	326	tys/µl*	139 - 387	
RDW-SD	40,8	fl*	35,1 - 43,9	
RDW-CV	11,8	%*	11,6 - 14,4	
PDW	13,7	fl*	9,8 - 16,1	
MPV	11,1	fl*	9,4 - 12,6	
P-LCR	34,5	%*	19,2 - 47,0	
PCT	0,36	%	0,16 - 0,35	H
Neutrofile	2,30	tys/µl*	1,78 - 6,04	
Limfocyty	3,25	tys/µl*	1,30 - 3,40	
Monocyty	0,53	tys/µl*	0,31 - 0,92	
Eozynofile	0,14	tys/µl*	0,03 - 0,39	
Bazofile	0,02	tys/µl*	0,01 - 0,09	
IG	0,01	tys/µl*	0,00 - 0,04	
NRBC	0,00	tys/µl*	0,00 - 0,03	
Neutrofile	36,8	%*	40,8 - 70,4	L
Limfocyty	52,0	%*	21,0 - 50,0	H
Monocyty	8,5	%*	5,1 - 11,2	
Eozynofile	2,2	%*	0,4 - 6,6	
Bazofile	0,30	%*	0,20 - 1,30	
IG	0,20	%*	0,00 - 0,50	
NRBC	0,00	%*	0,00 - 0,01	

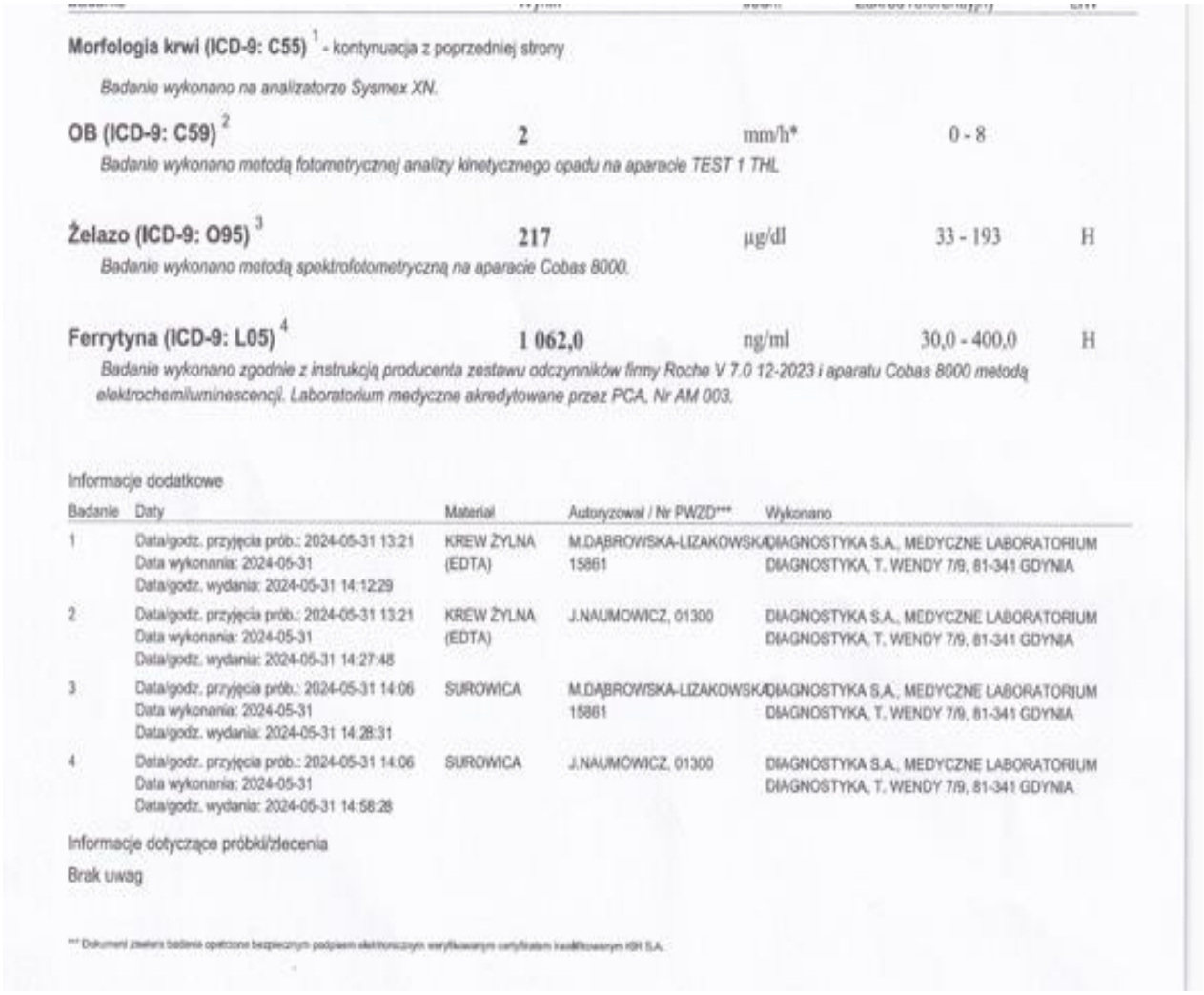
Strona: 1 z 2

[redacted]

DIAGNOSTA LABORATORYJNY

Data wygenerowania pdf/wydruku: 2024-05-31 14:05:28

Fig. 1. *Peripheral blood count with normal blood cell amount and hemoglobin, with slight macrocytosis and relative lymphocytosis with a reduced percentage of neutrophils.*



Morfologia krwi (ICD-9: C55) [1] - kontynuacja z poprzedniej strony

Badanie wykonano na analizatorze Sysmex XN.

OB (ICD-9: C59) [2]	2	mm/h*	0 - 8	

Badanie wykonano metodą fotometrycznej analizy kinetycznego opadu na aparacie TEST 1 THL

Żelazo (ICD-9: O95) [3]	217	µg/dl	33 - 193	H

Badanie wykonano metodą spektrofotometryczną na aparacie Cobas 8000.

Ferrytyna (ICD-9: L05) [4]	1 062,0	ng/ml	30,0 - 400,0	H

Badanie wykonano zgodnie z instrukcją producenta zestawu odczynników firmy Roche V 7.0 12-2023 i aparatu Cobas 8000 metodą elektrochemiluminescencji. Laboratorium medyczne akredytowane przez PCA, Nr AM 003.

Informacje dodatkowe

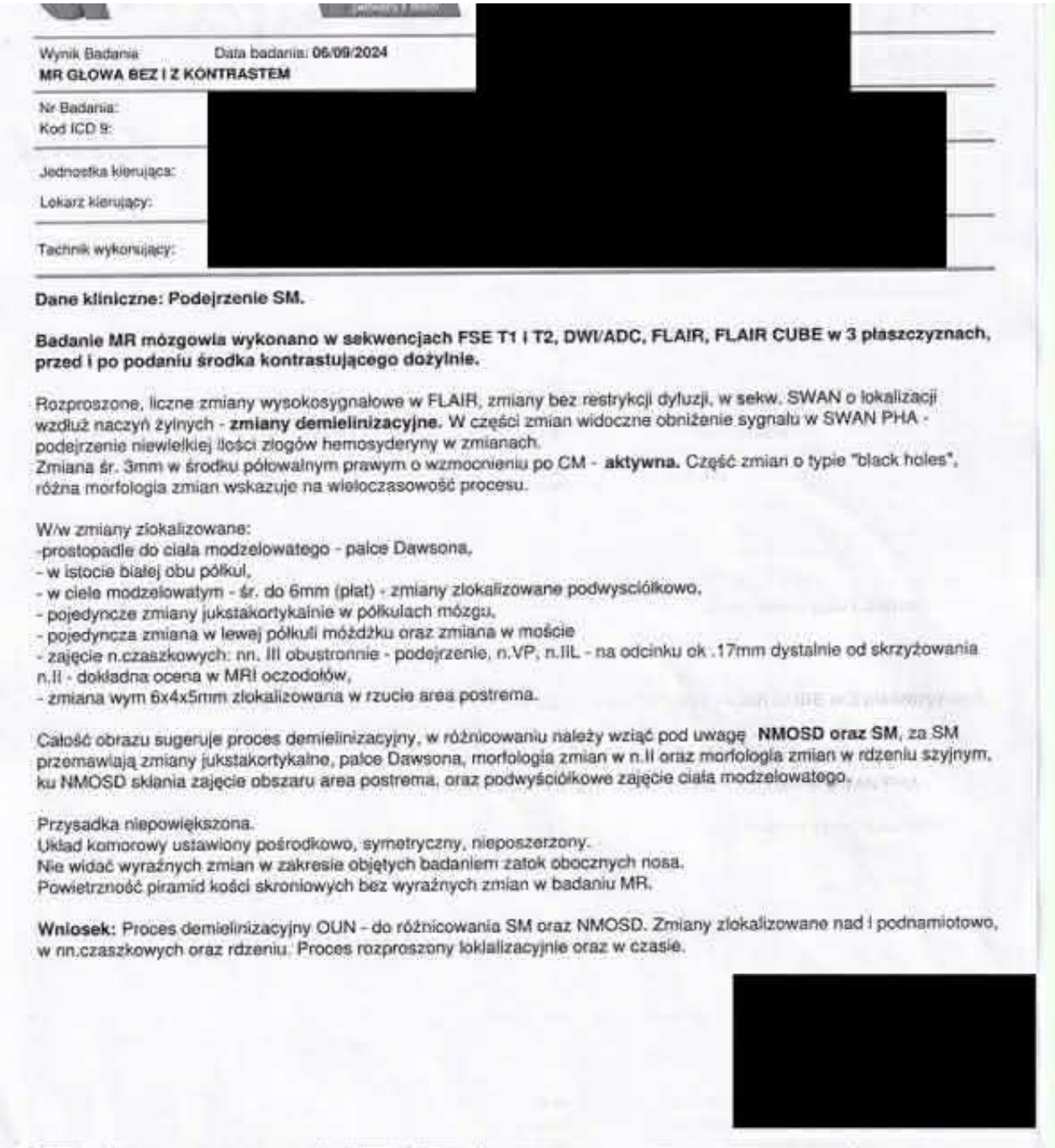
Badanie	Daty	Materiał	Autoryzował / Nr PWZD***	Wykonano
1	Data/godz. przyjęcia prób.: 2024-05-31 13:21 Data wykonania: 2024-05-31 Data/godz. wydania: 2024-05-31 14:12:29	KREW ŻYLNA (EDTA)	M.DĄBROWSKA-LIZAKOWSKA 15861	DIAGNOSTYKA S.A., MEDYCZNE LABORATORIUM DIAGNOSTYKA, T. WENDY 7/9, 81-341 GDYNIA
2	Data/godz. przyjęcia prób.: 2024-05-31 13:21 Data wykonania: 2024-05-31 Data/godz. wydania: 2024-05-31 14:27:48	KREW ŻYLNA (EDTA)	J.NAUMOWICZ, 01300	DIAGNOSTYKA S.A., MEDYCZNE LABORATORIUM DIAGNOSTYKA, T. WENDY 7/9, 81-341 GDYNIA
3	Data/godz. przyjęcia prób.: 2024-05-31 14:06 Data wykonania: 2024-05-31 Data/godz. wydania: 2024-05-31 14:28:31	SUROWICA	M.DĄBROWSKA-LIZAKOWSKA 15861	DIAGNOSTYKA S.A., MEDYCZNE LABORATORIUM DIAGNOSTYKA, T. WENDY 7/9, 81-341 GDYNIA
4	Data/godz. przyjęcia prób.: 2024-05-31 14:06 Data wykonania: 2024-05-31 Data/godz. wydania: 2024-05-31 14:58:28	SUROWICA	J.NAUMOWICZ, 01300	DIAGNOSTYKA S.A., MEDYCZNE LABORATORIUM DIAGNOSTYKA, T. WENDY 7/9, 81-341 GDYNIA

Informacje dotyczące próbki/zlecenia

Brak uwag

*** Dokument zawiera badania opatrzone bezpiecznym podpisem elektronicznym weryfikowanym certyfikatem kwalifikowanym ISH S.A.

Fig. 2. *Additional laboratory tests (ESR, iron, ferritin), which revealed significant deviations - significantly elevated ferritin and iron levels indicating an actual clinical problem not visible in the basic blood count.*



Wynik Badania Data badania: 06/09/2024
MR GŁOWA BEZ I Z KONTRASTEM

Nr Badania:
Kod ICD 9:

Jednostka kierująca:

Lekarz kierujący:

Technik wykonujący:

Dane kliniczne: Podejrzenie SM.

Badanie MR mózgowia wykonano w sekwencjach FSE T1 i T2, DWI/ADC, FLAIR, FLAIR CUBE w 3 płaszczyznach, przed i po podaniu środka kontrastującego dożylnie.

Rozproszone, liczne zmiany wysokosygnałowe w FLAIR, zmiany bez restrykcji dyfuzji, w sekw. SWAN o lokalizacji wzdłuż naczyń żylnych - **zmiany demielinizacyjne.** W części zmian widoczne obniżenie sygnału w SWAN PHA - podejrzenie niewielkiej ilości złogów hemosyderyny w zmianach.
Zmiana śr. 3mm w środku półowalnym prawym o wzmocnieniu po CM - **aktywna.** Część zmian o typie "black holes", różna morfologia zmian wskazuje na wieloczasowość procesu.

W/w zmiany zlokalizowane:
-prostopadle do ciała modzelowatego - palce Dawsona,
- w istocie białej obu półkul,
- w ciele modzelowatym - śr. do 6mm (płat) - zmiany zlokalizowane podwyściółkowo,
- pojedyncze zmiany jukstakortykalnie w półkulach mózgu,
- pojedyncza zmiana w lewej półkuli móżdżku oraz zmiana w moście
- zajęcie n.czaszkowych: nn. III obustronnie - podejrzenie, n.VP, n.IIL - na odcinku ok .17mm dystalnie od skrzyżowania n.II - dokładna ocena w MRI oczodołów,
- zmiana wym 6x4x5mm zlokalizowana w rzucie area postrema.

Całość obrazu sugeruje proces demielinizacyjny, w różnicowaniu należy wziąć pod uwagę **NMOSD oraz SM**, za SM przemawiają zmiany jukstakortykalne, palce Dawsona, morfologia zmian w n.II oraz morfologia zmian w rdzeniu szyjnym, ku NMOSD skłania zajęcie obszaru area postrema, oraz podwyściółkowe zajęcie ciała modzelowatego.

Przysadka niepowiększona.
Układ komorowy ustawiony pośrodkowo, symetryczny, nieposzerzony.
Nie widać wyraźnych zmian w zakresie objętych badaniem zatok obocznych nosa.
Powietrzność piramid kości skroniowych bez wyraźnych zmian w badaniu MR.

Wniosek: Proces demielinizacyjny OUN - do różnicowania SM oraz NMOSD. Zmiany zlokalizowane nad i podnamiotowo, w nn.czaszkowych oraz rdzeniu. Proces rozproszony loklalizacyjnie oraz w czasie.

Fig. 3. *Result of brain MRI performed without and with contrast, showing numerous demyelinating changes of a disseminated nature in time and space (including juxtacortical changes and characteristic Dawson's fingers) with one active lesion, corresponding to the image typical of multiple sclerosis.*

Genomed

Warszawa, dn. 2024-07-20

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Genomed S.A.
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WYNIK ANALIZY DNA

oryginał / kopia / duplikat

[redacted]

Lekarz kierujący
pacjent indywidualny
Oddział kierujący
nie dotyczy

Telefon kontaktowy
608 532 316
Adres kontaktowy
ul. Głogowa 4
84-100 Puck

NIP:
REGON:
Tel.:

Wskazania do wykonania badania
zaburzenia przemiany żelaza

Cel badania
Diagnostyka postnatalna. Weryfikacja rozpoznania klinicznego

Kod Kontraktowy

Data przyjęcia materiału do laboratorium
2024-07-03
Numer próbki
31558
Data zapisania materiału do badania
2024-07-02
Procedura
HFE-1
HFE-1: Hemochromatoza
Rodzaj materiału do badania
krew żylna

Wynik
Nieprawidłowy: HFE c.845G>A/ c.845G>A

Interpretacja i komentarz diagnostyczny

Stwierdzono obecność badanego patogennego wariantu c.845G>A p.Cys282Tyr (C282Y, rs1800562) w obu allelach genu HFE (w układzie homozygotycznym). Nie stwierdzono obecności innych patogennych wariantów w badanych regionach genu HFE.

Genotyp HFE zgodny z HGVS: LRG_748t1:c.845G>A(;)(845G>A)

Wynik badania molekularnego, w przypadku występowania objawów choroby, potwierdza rozpoznanie kliniczne klasycznej postaci HFE-zależnej hemochromatozy wrodzonej.

Wynik badania jest wskazaniem do wykonania badań nosicielstwa zidentyfikowanego wariantu c.845G>A p.Cys282Tyr (C282Y) w rodzinie Pacjenta, z uwagi na podwyższone ryzyko wystąpienia objawów klinicznych hemochromatozy u nosicieli homozygotycznego wariantu c.845G>A p.Cys282Tyr (C282Y).

Wskazana jest konsultacja w Poradni Genetycznej lub innej właściwej poradni specjalistycznej w celu omówienia wyniku i ustalenia dalszego postępowania.

Informacje dodatkowe:
Przeprowadzono analizę sekwencji eksonów 2 i 4, wraz z sąsiadującymi sekwencjami intronowymi, w kierunku obecności patogennego wariantu c.845G>A p.Cys282Tyr (C282Y) i wariantu c.187C>G p.His63Asp (H63D) oraz innych wariantów patogennych korelowanych z hemochromatozą, występujących w badanych regionach genu HFE. Analizę przeprowadzono z zastosowaniem techniki sekwencjonowania DNA metodą Sangera.

Sekwencja genu HFE wg Locus Reference Genomic, nazwa genu wg HGNC, zapis genotypu wg HGVS v20.05. W nawiasach podano zwyczajowy zapis wariantów.

Zastosowana metoda diagnostyczna umożliwia identyfikację najczęstszych patogennych wariantów c.845G>A p.Cys282Tyr (C282Y) i c.187C>G, p.His63Asp (H63D), stwierdzanych u 83-99% pacjentów z rozpoznaniem

Strona 1

NZOZ GENOMED
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tel. +48 22 644 60 19, faks +48 22 644 60 25

Fig. 4. *DNA analysis result showing the presence of a pathogenic variant of the HFE gene (c.845G>A, p.Cys282Tyr) in a homozygous pattern, confirming the genetic basis of hemochromatosis.*

Following the implementation of immunomodulatory therapy and phlebotomy, the parameters of metabolism improved. Ferritin concentration decreased from 1062 ng/ml to 199 ng/ml. However, despite treatment, neurological symptoms persisted, including impaired proprioception, chronic fatigue, and dizziness.

Discussion

This case highlights a potential bond between hereditary hemochromatosis and multiple sclerosis. The evidence gathered suggests that disturbances in iron metabolism might be involved in the pathogenesis of neurodegenerative diseases, including multiple sclerosis [5,6].

One of the key mechanisms that may link both diseases, is exorbitant iron accumulation in the central nervous system. Iron, an element with high redox potential, promotes the formation of reactive oxygen species, increasing oxidative stress and leading to deal damage to lipids in cell membranes, oligodendrocytes, and myelin [5]. Ferroptosis, a regulated form of iron-dependent cell death, whose importance is increasingly emphasized in neurodegenerative and demyelinating processes [5,7], may also play a significant role.

Imaging studies have shown an inflated iron deposition inside deep brain structures in patients with multiple sclerosis, particularly in the basal ganglia and thalamus [6,8]. The degree of iron accumulation may correlate with disease activity and the severity of neurological deficits. The coexistence of hemochromatosis might potentially accelerate these processes, through chronic exposure of the central nervous system to increased iron levels.

Hereditary hemochromatosis, mostly associated with the mutation of C282Y section of the HFE gene, leads to increased iron absorption from the gastrointestinal tract and its deposition in various organs. Although classically this disease is primarily associated with damage to the liver, pancreas, and heart, its potential neurological consequences are increasingly being recognized [9].

In this case, the long-term unrecognized iron overload, appears to be particularly significant. It is possible that chronic oxidative stress, associated with iron inflation, influenced the development or progression of demyelinating processes, long before the full-blown disease manifested. Early neurological symptoms, such as an episode of double vision in 2018, may have been consistent with an earlier flare of demyelinating disease.

It's worth noting the potential impact of hemochromatosis treatment on the course of the neurological disease. Regular bloodletting has led to a significant deflation of ferritin levels, which theoretically could limit the occurrence of oxidative stress and neurodegenerative processes. Moreover, currently there is no clear clinical data, that could confirm of iron overload treatment affecting the course of multiple sclerosis.

This case also highlights the importance of extensive laboratory and imaging diagnostics in patients presenting nonspecific neurological symptoms. Early detection of iron metabolism disorders managed to lead the diagnosis towards hemochromatosis and the implementation of treatment before severe organ damage happened.

In summary, the presented case could support the hypothesis of a biological link between iron metabolism disorders and multiple sclerosis. However, it still shows the inability to allow a definitive conclusion, as to whether it’s the cause of observed coincidence. Further research consisting of genetic, imaging, and bioinformatics diagnosis is necessary, to better define the role of iron in the pathogenesis of multiple sclerosis and the potential role of hemochromatosis as a factor modifying the course of the disease.

Conclusions

Retardations of iron homeostasis in brain are a significant component of the aging process and the pathogenesis of many neurodegenerative diseases. Excessive iron accumulation promotes the formation of reactive oxygen species, increases oxidative stress, induces ferroptosis, and activates inflammatory processes, leading to nerve cell damage and the progression of neurodegenerative changes.

In multiple sclerosis, increased iron deposition takes place both in gray matter (basal ganglia) and in white matter (demyelinating lesions). Shown evidence suggests that disturbances in iron metabolism are not merely accompanying neurodegeneration but may actively participate in the mechanisms of demyelination and central nervous system damage.

The presented case may indicate a potential connection between hereditary hemochromatosis and multiple sclerosis. Long-term iron overload may have been a factor in the exacerbation of neurodegenerative and demyelinating processes. However, it is not possible to definitively determine whether the coexistence of both conditions is causal or merely coincidental.

Modern MRI techniques and the development of genetic and bioinformatics research may opt for more precise definition of the role of iron in the pathogenesis of multiple sclerosis in the future. Further clinical studies are required, to assess the impact of chronic iron overload on the development course of demyelinating diseases and the potential role of iron-reducing therapies.

REFERENCES

1. Dusek, P., Hofer, T., Alexander, J., Roos, P. M., & Aaseth, J. O. (2022). Cerebral iron deposition in neurodegeneration. *Biomolecules, 12*(5), 714. https://doi.org/10.3390/biom12050714
2. Singh, P., Millson, C., & Driver, R. (2024). Hereditary haemochromatosis: A review. *Journal of the Royal College of Physicians of Edinburgh, 54*(4), 340–347. https://doi.org/10.1177/14782715241298724
3. Tang, C., Yang, J., Zhu, C., Ding, Y., Yang, S., Xu, B., & He, D. (2024). Iron metabolism disorder and multiple sclerosis: A comprehensive analysis. *Frontiers in Immunology, 15*, 1376838. https://doi.org/10.3389/fimmu.2024.1376838
4. Stockwell, B. R., Friedmann Angeli, J. P., Bayir, H., Bush, A. I., Conrad, M., Dixon, S. J., Fulda, S., Gascón, S., Hatzios, S. K., Kagan, V. E., Noel, K., Jiang, X., Linkermann, A., Murphy, M. E., Overholtzer, M., Oyagi, A., Pagnussat, G. C., Park, J., Ran, Q., . . . Zhang, D. D. (2017). Ferroptosis: A regulated cell death nexus linking metabolism, redox biology, and disease. *Cell, 171*(2), 273–285. https://doi.org/10.1016/j.cell.2017.09.021
5. Stephenson, E., Nathoo, N., Mahjoub, Y., Dunn, J. F., & Yong, V. W. (2014). Iron in multiple sclerosis: Roles in neurodegeneration and repair. *Nature Reviews Neurology, 10*(8), 459–468. https://doi.org/10.1038/nrneurol.2014.118
6. Ward, R. J., Zucca, F. A., Duyn, J. H., Crichton, R. R., & Zecca, L. (2014). The role of iron in brain ageing and neurodegenerative disorders. *The Lancet Neurology, 13*(10), 1045–1060. https://doi.org/10.1016/S1474-4422(14)70117-6
7. Hagemeier, J., Weinstock-Guttman, B., Bergsland, N., Heininen-Brown, M., Carl, E., Kennedy, C., . . . Zivadinov, R. (2018). Iron deposition in multiple sclerosis measured by susceptibility-weighted imaging filtered phase: A case-control study.
8. Nandar, W., & Connor, J. R. (2011). HFE gene variants affect iron in the brain. *The Journal of Nutrition, 141*(4), 729S–739S. https://doi.org/10.3945/jn.110.130351
9. Pichler, I., Del Greco M., F., Gögele, M., Lill, C. M., Bertram, L., Do, C. B., Eriksson, N., Foroud, T., Myers, R. H., PD GWAS Consortium, Nalls, M. A., Keller, M. F., International Parkinson's Disease Genomics Consortium, Wellcome Trust Case Control Consortium 2, Benyamin, B., Whitfield, J. B., Genetics of Iron Status Consortium, Pramstaller, P. P., Hicks, A. A., . . . Thompson, J. R. (2013). Serum iron levels and the risk of Parkinson disease: A Mendelian randomization study. *PLoS Medicine, 10*(6), e1001462. https://doi.org/10.1371/journal.pmed.1001462
10. World Medical Association. (2024). *WMA Declaration of Helsinki—Ethical principles for medical research involving human participants*. https://www.wma.net/policies-post/wma-declaration-of-helsinki/