CASE REPORT

Annals of Agricultural and Environmental Medicine 2022, Vol 29, No 2, 309–315
www.aaem.pl

Multiple sclerosis in a child with neurofibromatosis type I – clinical management of a challenging case

Kamil Kośmider[1,A-D,F], Agata Kozakiewicz[1,B,D,F], Aleksandra Filipiuk[1,B,D,F], Dorota Sławińska[2,B-C,F], Monika Lejman[3,A,E-F], Joanna Zawitkowska[2,A,E-F]

[1] *Student Scientific Society, Department of Paediatric Haematology, Oncology and Transplantology, Medical University, Lublin, Poland*
[2] *Department of Paediatric Haematology, Oncology and Transplantology, Medical University, Lublin, Poland*
[3] *Laboratory of Genetic Diagnostics, Department of Paediatric Haematology, Oncology and Transplantology, Medical University, Lublin, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Kośmider K, Kozakiewicz A, Filipiuk A, Sławińska D, Lejman M, Zawitkowska J. Multiple sclerosis in a child with neurofibromatosis type I – clinical management of a challenging case. Ann Agric Environ Med. 2022; 29(2): 309–315. doi: 10.26444/aaem/142267

Abstract

A 13-year-old girl with neurofibromastosis (NF1) was admitted to the Department of Paediatric Haematology, Oncology and Transplantology due to progressive vision loss in September 2018. The patient was diagnosed with optic nerve gliomas and chemotherapy was initiated. During the treatment, the girl experienced muscle weakness in the lower limbs, and uncharacteristic lesions were detected in the spinal cord. Eventually, the girl was diagnosed with MS. The described case is one of the few reports of a child with coexisting NF1 and MS. The coincidence of these diseases is unusual and requires a multidisciplinary approach. Vision impairment in patients suffering from NF1 is typically associated with optic nerve gliomas, although it can be caused by other factors, such as MS, which is proven to have a higher prevalence in the NF1 population. Extensive ophthalmological diagnostics may not be conclusive, thus there is a need for the thorough neurological evaluation of patients with NF1 and visual deficits.

Key words

case report, central nervous system, demyelination, neurofibromatosis type 1, multiple sclerosis

INTRODUCTION

Neurofibromatosis type 1 (NF1, von Recklinghausen disease) is an autosomal dominant disorder characterized by the presence of numerous benign tumours of the nervous system [1]. The term 'neurofibroma' was introduced in 1881 by Friedrich Daniel von Recklinghausen, and initially there was only one condition known as neurofibromatosis [2]. However, at the end of the twentieth century different forms of the disease were identified (neurofibromatosis type 2, schwannomatosis) [3].

NF1 is a consequence of a genetic alteration in the *NF1* gene (locus 17q11.2) and specific mutations can be identified in over 95% of patients, Although genetic testing is not obligatory in the diagnostics, it can be helpful in case of ambiguous clinical presentation of the disease [4]. A wide spectrum of NF1 anomalies have been found, including splice site mutations (28%), reading-frame shift (24%), nonsense mutations (21%), missense and/or 1 to 8 amino acid deletions/duplications (19%), whole gene deletions (4%), intragenic exon deletions/duplications (3%), and others (<1%), such as balanced translocations, all leading to dysfunction of neurofibromin, a tumour suppressor and a product of the *NF1* gene [4]. The lack of neurofibromin's s protective function leads to increased risk of benign and malignant tumours, especially in the nervous system [5]. The newest data obtained in Finland shows that NF1 is much more common than previously estimated, with a birth incidence of about 1/2000 and a general prevalence of 1/4000 [6, 7].

Diagnosis is based on criteria developed in 1988 by National Institutes of Health (NIH), at least 2 of them must be met in order to diagnose NF1 (Tab. 1) [8]. However, in May 2021, a new proposal was published for the NF1 diagnostic criteria (Tab. 2) [9], which were developed using the modified Delphi method with the participation of global NF experts, non-NF specialists, as well as patients, foundations and patient advocacy organisations. Especially noteworthy is the introduction of genetic testing in the NF1 diagnostics, which was not present in the NIH criteria. This innovation will allow clinicians to diagnose NF1 and treat potential

Table 1. NIH criteria for diagnosis of NF1 [8]

1. At least 6 *café-au-lait* spots greater than 5 mm in diameter before puberty, or over 15 mm in post-pubertal individuals.
2. Two or more neurofibromas of any type, or one plexiform neurofibroma.
3. Freckling in the axillary (Crowe sign) or inguinal regions.
4. Optic glioma.
5. Two or more Lish nodules.
6. A distinctive bone lesion with sphenoid dysplasia, or thinning of the long bone cortex with or without pseudarthrosis.
7. A first-degree relative (parent, sibling, or offspring) who meets NIH criteria.

Adress for correspondence: Kamil Kośmider, Student Scientific Society, Department of Paediatric Haematology, Oncology and Transplantology, Medical University, Lublin, Poland
E-mail: kamilkosmider96@gmail.com

Received: 21.05.2021; accepted: 14.09.2021; *first published: 30.09.2021*

Table 2. Revised diagnostic criteria for NF1 [9]

A. The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1, if 2 or more of the following are present: • Six or more café-au-lait macules over 5 mm in prepubertal individuals, and over 15 mm in postpubertal individuals.[1] • Freckling in the axillary (Crowe sign) or inguinal region.[1] • Two or more neurofibromas of any type or one plexiform neurofibroma. • Optic glioma. • Two or more Lish nodules identified by slit lamp examination, or 2 or more choroidal abnormalities – defined as bright, patchy nodules imaged by optical coherence tomography/near-infrared reflectance imaging. • A distinctive bone lesion, such as sphenoid dysplasia[2], anterolateral bowing of the tibia, or pseudarthrosis of a long bone. • A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue, such as white blood cells.
B. The child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

[1] If only *café-au-lait* macules and freckling are present, the diagnosis is most likely NF1, but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the 2 pigmentary findings (*café-au-lait* macules or freckling) should be bilateral.
[2] Sphenoid wing dysplasia is not a separate criterion in the case of an ipsilateral orbital plexiform neurofibroma.

complications in more individuals. For instance, the authors of these criteria recommend that genetic testing should be performed in patients with segmental clinical findings, in families with at least 2 affected siblings and unaffected parents, and finally in children in which NF1 is diagnosed based only on pigmentary lesions. Moreover, DNA analysis in more NF1 patients will hopefully result in the detection of new pathological *NF1* variants, especially those associated with atypical or severe course of the disease [9].

Optic pathway glioma (OPG) is the most common tumour occurring in children suffering from NF1, with an estimated prevalence of 15% – 20%, although up to 50% of cases might be asymptomatic [10, 11, 12, 13]. OPGs associated with NF1 are mostly identified in younger children, as they can be found in 22% patients under 10 years of age, whereas in patients aged 10–19.9 years, OPGs occur in 10–15% of cases [11]. Optic nerves are most often affected, whereas optic chiasm and the retrochiasmatic region of the optic pathway are less frequent locations of OPGs [11, 12]. Optic nerve gliomas (ONGs) are manifested by visual acuity (VA) and visual field (VF) defects, papilledoema, strabismus or relative afferent pupillary defects [13].

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) with a ranging prevalence from 140/100,000 in North America and 108/100,000 in Europe to 2.1 and 2.2/100,000 in Sub-Saharan Africa and East Asia, respectively [14, 15]. The majority of cases are diagnosed in adult patients, with paediatric onset MS occurring in 1.7% – 5.6% of all MS patient, with the majority of the children suffering from the relapsing-remitting form of MS [15].

It has been proven that there is a relationship between NF1 and the higher incidence of certain neurological diseases, such as epilepsy, headache and sleep disorders [16]. This case report presents the details of a paediatric patient suffering from NF1 who was also diagnosed with MS. The diagnostic process and challenges in differential diagnosis are described, highlighting how the symptoms of MS can resemble clinical manifestations of NF1, which may delay diagnosis and negatively affect the patient's outcome. The current state of knowledge regarding the link between NF1 and MS and possible causes of that association are also reviewed.

CASE REPORT

A 13-year-old girl with NF1 was admitted to the Department of Paediatric Haematology, Oncology and Transplantology due to rapid deterioration in VA and VF in September 2018. The child had been previously diagnosed with epilepsy and treated with valproic acid. Both parents also suffered from NF1. Physical examination revealed features of NF1, such as *Café-au-lait* spots and axillary and inguinal freckling (Crowe's sign). The multi-disciplinary diagnostic process of the patient as well as the applied treatment and results of magnetic resonance imaging (MRI) are presented in Table 3. The girl was finally diagnosed with MS and is currently undergoing therapy with dimethyl fumarate, which has resulted in an improvement in her neurological condition.

DISCUSSION

The girl underwent a long diagnostic process carried out in various departments at different medical centres. There are several reasons for that, one of the most notable being the fact that diagnosing MS in paediatric population poses a significant challenge for physicians. Data obtained during a nationwide study conducted in Germany has proved, that MS in children is a very rare event, with estimated incidence of 0.65/100,000 children [17]. One of the characteristic red flag symptoms of a demyelinating disease in patients below the age 18 of years is VA and VF impairment. Optic neuritis is proven to be an initial finding in 14% – 35% of children suffering from MS [15].

Beginning in November 2017, the presented patient experienced deterioration of VA and VF. Initial diagnostics including MRI, ophthalmological consultation, as well as electroretinography and visual evoked potential test, did not indicate the cause of the progressive vision loss. However, re-examination performed in our Department in September 2018 revealed lesions characteristic of ONGs. Adequate therapy of ONGs using vinblastine (VBL) led to improvement in the patient's vision and reduction in optic nerves diameters, despite the premature discontinuation of the treatment. Further improvement was obtained after the initiation of MS treatment. This indicated that VA and VF impairment could have been the consequence of coexisting ONGs and optic neuritis in the course of the MS.

Visual evoked potential tests play an important role in paediatric MS diagnosis but, unfortunately, in the described case they failed to reveal demyelinating process occurring in the optic nerves; therefore, at that stage, MS was not considered as a possible cause [15]. Moreover, deterioration of the girl's neurological condition could have been a consequence of VBL chemotherapy, as well as intramedullary astrocytomas. VBL is known to cause mild neuropathy; however, a case of severe neurotoxicity leading to disability in a 20-year-old female patient was also reported [18]. It was decided to reduce the dose, and eventually discontinue treatment, but deterioration of the patient's condition led to further diagnostics. Additional tests were performed, including MRI of the spinal cord in March 2019 (Fig. 1–2) and a cerebrospinal fluid (CSF) examination in September 2019. Uncharacteristic lesions in the spinal cord described at the time as possible intramedullary astrocytomas were misleading, especially considering that the diagnosis of

Table 3. Diagnostics and treatment of the patient

Period	Department	Clinical background	Diagnostic tests results including magnetic resonance imaging (MRI)	Current diagnosis	Applied treatment	Treatment results
October 2010	Department of Paediatric Otolaryngology	The patent was admitted to hospital in order to undergo tonsillectomy and suffered a generalized tonic-clonic seizure during induction of anaesthesia.	Electroencephalogram (EEG) monitoring revealed generalised paroxysmal abnormalities. Computed tomography of the cerebrum revealed no abnormality.	Epilepsy.	Successful chronic treatment with valproic acid (VPA) at the dose of 200 milligrams (mg) per os (p.o.) twice a day.	No further seizures were reported during VPA treatment.
November 2017	Department of Paediatric Neurology	Severe headache and progressive VA (visual acuity) and VF (visual field) deterioration. Occurrence of characteristic symptoms, such as numerous *Café-au-lait* spots, Crowe's sign, along with a positive family history, led to the diagnosis of neurofibromatosis type 1 (NF1). The patient was referred to the Department of General Ophthalmology.	MRI of cerebrum demonstrated hamartomatous changes within the deep brain structures and in the mesencephalon, characteristic for NF1.	Neurofibromatisis type I.	Discontinuation of VPA.	Patients did not suffer from seizures despite discontinuation of the anti-epileptic treatment.
November 2017	Department of General Ophthalmology	Thepatient was diagnosed with optic neuropathy of unknown etiology.	On the basis of molecular genetic testing, Leber's hereditary optic neuropathy was excluded.	Neurofibromatisis type I. Optic neuropathy of unknown etiology.	Intravenous (i.v.) methylprednisolone (2x 250 mg).	Temporary improvement in VA and VF was achieved.
March 2018	Department of General Ophthalmology	The patient underwent electroretinography and visual evoked potential test which supported the diagnosis of optic neuropaty, but did not allow determination of the exact cause of the condition.	Visual evoked potential test revealed prolongation of P100 latency and reduced aplitudes in both eyes.	Neurofibromatisis type I. Optic neuropathy of unknown etiology.		
September 2018	Department of Paediatric Haematology, Oncology and Transplantology	On the basis of imaging examinations and neurosurgical consultation, as well as the patient's rapidly deteriorating condition and coexisting NF1, optic gliomas were diagnosed and chemotherapy was initiated. After a month there was a worsening in the patient's general condition and the girl began to suffer from abdominal pain, loss of appetite and weight loss, pain and muscle weakness in the lower limbs, leading to movement impairment; hence, the dose of vinblastine (VBL) was reduced by 50%. Despite the reduction in the dose of VBL, there was a further deterioration in the neurological condition, causing immobilization of the patient.	MRI scans of the cerebrum showed dilatation of the optic nerves (left 6mm, right 5mm), indicating optic nerve gliomas. Observed lesions were not contrast-enhancing, as proven after administration of gadolinium-based contrast.	Neurofibromatosis type I. Optic gliomas.	VBL i.v. at the dose of 9 mg instead of the most common first-line treatment for low grade glioma, consisting of vincristine and carboplatin, due to lower toxicity of VBL compared to standard first-line drugs. The dose was reduced to 4.5 mg i.v. after a month of therapy due to deterioration of the patient's neurological condition.	There was a significant improvement in VA and VF, and no further deterioration of vision occured.
March 2019	Department of Paediatric Haematology, Oncology and Transplantology	The patient's neurological condition worsened; chemotherapy was therefore discontinued. MRI was performed and hospitalization in the Department of Child Neurology planned.	Previously diagnosed dilatation of the optic nerves and their asymmetry were not found in the MRI scans of the cerebrum. MRI of the spinal cord revealed poorly demarked high-intensity focal lesions in the spinal cord on T2-weighted images, one at the C2/C3 level (27x8 mm), the other at the C4/C5 level (29x6mm). Moreover, minor foci were also found in the thoracic and lumbar sections of the spinal cord. It was concluded that these lesions were most likely intramedullary astrocytomas; however, other pathologies were not excluded.	Neurofibromatosis type I. Optic gliomas.	Discontinuation of the chemotherapy due to further worsening in the patient's neurological condition.	Stabilization in VA and VF was achieved.

Table 3. Diagnostics and treatment of the patient (continuation)

Period	Department	Clinical background	Diagnostic tests results including magnetic resonance imaging (MRI)	Current diagnosis	Applied treatment	Treatment results
July 2019	Department of Child Neurology	During the neurological examination, bilateral pyramidal symptoms (Babinski reflex, Chaddock reflex) were revealed.	Results of MRI were similar to those of the study performed in March 2019.	Neurofibromatosis type I. Optic gliomas.		
September - October 2019	Department of Paediatric Haematology, Oncology and Transplantology	Further neurological worsening occurred, the patient suffered from urinary hesitancy and paraesthesia of the upper and lower limbs.	Serologic tests (ELISA and Western Blot) for Lyme disease were performed but no IgG and IgM antibodies against Borrelia burgdorferi were detected. A lumbar puncture was performed and the cerebrospinal fluid (CSF) examined. There were no Borrelia burgdorferi-specific antibiodies in the CSF, nor were antibodies to aquaporin-4 found in serum. Therefore, neuroborreliosis and neuromyelitis optica (Devic's disease) were excluded. There were, however, oligoclonal IgG bands in the CSF.	Neurofibromatosis type I. Optic gliomas.		
October 2019	Department of Paediatric Haematology, Oncology and Transplantology	Multi-disciplinary council with the participation of a neurologist, radiologist and physicians from our department took place, during which, taking into consideration changes in the latest MRI scans, oligoclonal bands in the CSF and the course of the disease, it was concluded that the patient's symptoms were of strictly neurological origin. Therefore, it was decided to continue diagnostics at the Department of Neurology and Epileptology.	MRI scans revealed that new well-delimited hyperintense lesions had appeared in the spinal cord. Moreover, the old lesions were better demarked than before. Relatively fast progress of radiological changes gave rise to the suspicion of an ongoing demyelinating process in the central nervous system.	Neurofibromatosis type I. Optic gliomas. Unspecified demyelinating disease of the central nervous system.		
November 2019	Department of Neurology and Epileptology	The patient suffered from gait disturbances and difficulties in initiating micturition. Bilateral pyramidal signs were present (Babinski and Chaddock reflexes), Romberg test was positive. Deviation of the tongue to the right was also found. There was severe weakness and hyperreflexia in the lower extremities. Based on the MRI results, presence of the oligoclonal bands in the CSF and the clinical presentation the patient was diagnosed with multiple sclerosis and proper therapy was initiated.		Neurofibromatosis type I. Optic gliomas. Multiple sclerosis.	Methylprednisolone (500 mg i.v.) for 5 days. Chronic treatment with dimethyl fumarate was initiated (2x240 mg p.o. per day).	After applied treatment, the patient's neurological condition improved, especially in gait and micturition.
April 2020	Department of Neurology and Epileptology	Neurological examination revealed deviation of the tongue to the right, positive bilateral Babinski sign, hyperreflexia in the lower extremities, positive Romberg test. The patient was able to move independently, there were no micturition disorders, VA and VF were partially recovered.	Results of MRI were similar to those of the study performed in October 2019.	Neurofibromatosis type I. Optic gliomas. Multiple sclerosis.	Treatment with dimethyl fumarate (2x240 mg p.o. per day) was sustained.	The patient's neurological condition was stabilized; therefore, the patent was treated with dimethyl fumarate ever since.

MS is largely based on an MRI examination [15]. However, detection of oligoclonal IgG bands in CSF was suggestive for the acquired demyelinating syndrome (ADS), as oligoclonal IgG bands are detected in 68% of ADSs cases in children from 12–17 years of age [19]. This group of diseases include paediatric MS, acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disease (NMOSD) and clinically isolated syndrome (CIS). Oligoclonal IgG bands are proven to be highly predictive of ADSs in this age group (positive predictive value: 0.89; 95% CI: 0.82–0.94; P <0.0001) [19]. NMOSD was considered as a possible cause of neurological symptoms, given the fact that the patient suffered from bilateral vision impairment, combined with manifestations of CNS damage and pathological changes in the spinal cord. However, IgG antibodies to aquaporin-4 (AQP4-IgG) in serum were not found. AQP4-IgG are highly specific for NMOSD, although according to international consensus, in the diagnostic criteria for NMOSD which

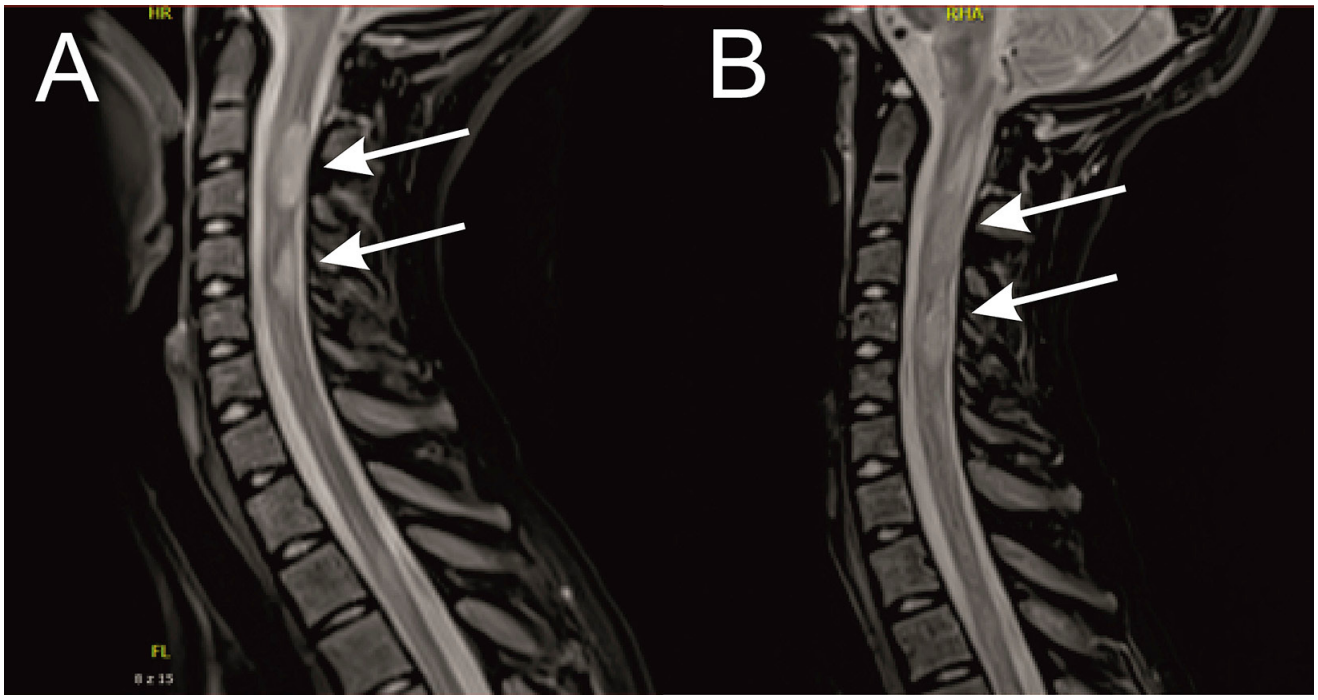

Figure 1. Cervical spine MRI

are applicable in paediatric patients, there is a possibility to diagnose NMOSD without detection of these antibodies [20]. Nevertheless, red flag symptoms which signal the possibility of an alternative to NMOSD diagnoses were observed. Most noticeably, the girl suffered from neurological deterioration that progressed over the months (e.g. progressive worsening occurred between October 2018 – March 2019). Such a course of the disease is rarely seen in patients suffering from NMOSD (1%–2%) and is rather associated with MS. In NMOSD neurological worsening occurs during attacks. Furthermore, MRI findings were also more suggestive of MS, as lesions in the spinal cord (Fig. 1–2) do not exceed 3 adjacent segments, whereas in NMOSD longitudinally extensive transverse myelitis (LETM) in the spinal cord involving at least 3 contiguous segments is characteristic [20]. NMOSD was therefore rejected as a cause of the deteriorating neurological condition. Another disease excluded during differential diagnostics was Lyme disease as no IgG and IgM antibodies against Borrelia burgdorferi in CSF were found.

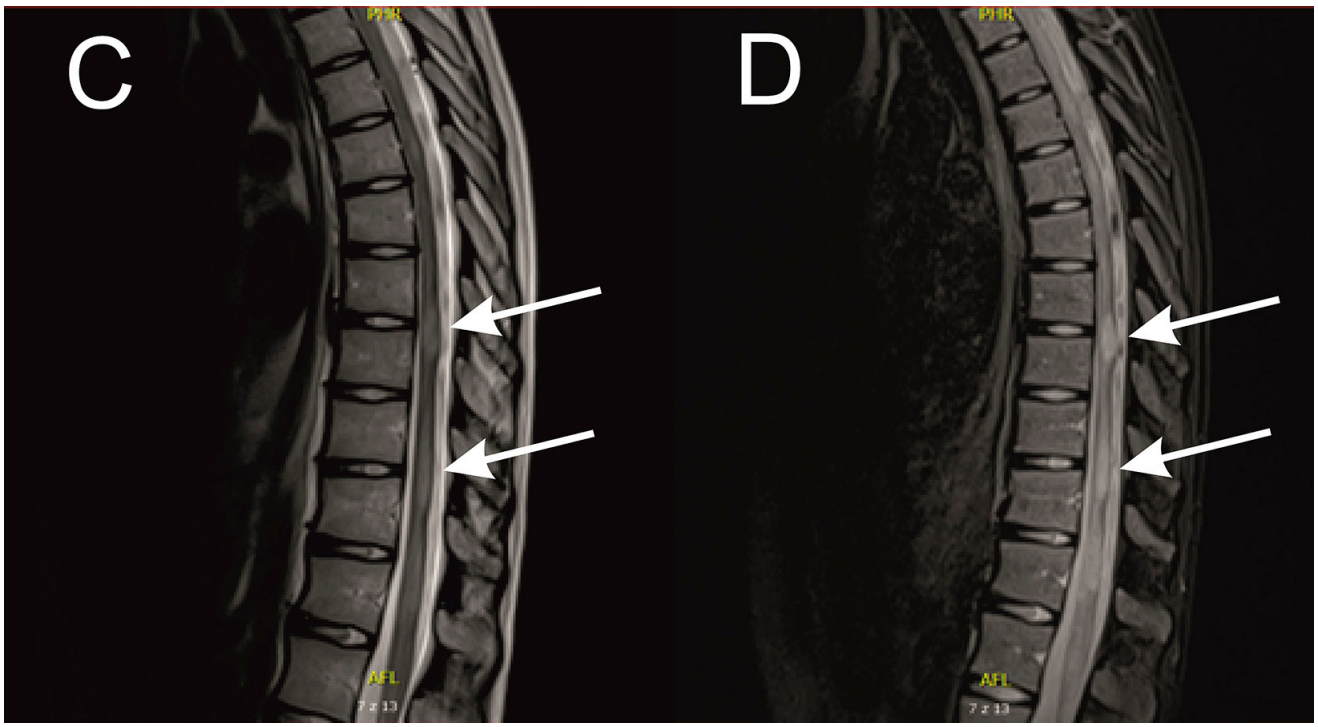

Figure 2. Thoracic spine MRI

In the described patient, during the course of the disease, clinical CNS events which resulted in deterioration of the patient's neurological condition were observed. In October 2019, the patient's symptoms were reassessed during a multidisciplinary council and it was concluded that VA and VF deterioration, previously viewed only as a manifestation of ONG, was in fact a consequence of bilateral gliomas as well as the first manifestation of ADS. In October 2018, relapse was observed when the girl experienced severe muscle weakness in the lower limbs which eventually led to immobilization. In September and October 2019, the patient experienced another relapse which caused urinary retention as well as paraesthesia of the upper and lower limbs. This worsening was combined with radiological progression, as in October 2019 new T2 hyperintense lesions had appeared in the spinal cord. According to the International Pediatric Multiple Sclerosis Study Group criteria for paediatric MS, at least two nonecephalophatic (not associated with consciousness or behavioural disturbances unexplained by fever or systemic illness) clinical CNS events separated by no less than 30 days and involving 2 separate CNS regions are sufficient to identify this disease. The girl was therefore diagnosed with MS and proper treatment was initiated [21].

Both NF1 and paediatric MS are rare diseases; therefore the question arises whether there is an association between a mutation in the *NF1* gene and increased risk of developing MS. So far, only 2 cases of children with coexisting NF1 and MS have been reported; however, in both cases, neither a detailed clinical picture nor the differential diagnosis were presented [22].

An analysis of the private insurers' database conducted in the USA between 2006–2010 showed that among 8,579 NF1 patients, 25 (0.3%) suffered from MS. This is a greater proportion compared to the non-NF1 population, in which of the 85,615 people, only 108 (0.1%) had MS. However, the study had limitations: the obtained data was based on the International Classification of Diseases (ICD) codes used for insurance claims, and not on full medical records. As the authors of the study emphasize, coding errors could undermine the results of the entire study [16]. It is also worth noting that the seizure the girl experienced at the age of 5 could be related to NF1. It was proven that patients suffering from NF1 are much more likely to also have epilepsy [16].

Another interesting study was conducted at the *French National Referral Centre for Neurofibromatosis* in Paris, where an analysis of 1,507 adult patients with NF1 showed that patients with the *NF1* mutation had more than twice the prevalence of MS (3.3/1,000), compared to the general French population (1.5/1000). Unfortunately, the small sample size and the fact that the study was carried out in a specialized medical centre in which patients with comorbidities of NF1 were more likely to seek help, were serious downsides of that study [23]. Therefore, the link between NF1 and MS remains uncertain.

There are 3 main hypotheses to explain the greater incidence of MS among patients suffering from NF1 [24]. The first is related to the embedding of the oligodendrocyte-myelin glycoprotein (OMG) gene within the intron 27b of the *NF1* gene [24]. OMG takes part in the myelination of nerves in the CNS and it was believed that its malfunction might cause MS. This hypothesis was called into question by a study in which *OMG* genes in 4 patients with coexisting NF1 and MS were analysed. Genetic alterations were discovered in 2 patients, whereas in the other 2, no pathologies were revealed. It was concluded that a mutation in the *OMG* gene is not sufficient for a person to develop MS [25].

The second hypothesis is based on the fact that *NF1* is expressed in oligodendrocytes, which are the target of autoimmunological reaction in the course of MS. Mutations in the *NF1* gene in zebrafish and mice are associated with increased oligodendrocyte precursor cells [24]. Moreover, *NF1* dysfunction in genetically-engineered mouse models lead to impairment of nitric oxide-mediated blood-brain barrier function. These factors could promote an auto-immunological reaction in the CNS [24].

The third explanation concerns the abnormal Schwann cell proliferation caused by a loss of *NF1* function [24]. Increased exposure to antigens expressed in peripheral myelin may activate auto-aggression towards them. Given that some of the Schwann cell antigens are shared with antigens in oligodendrocytes, it is possible that a cross-reaction is responsible for auto-immune demyelination in the CNS. The possible over-reactivity of the immune system in the course of NF1 could also be of importance [24].

CONCLUSIONS

The coincidence of NF1 and MS is a very rare phenomenon which requires thorough diagnostics. Effective cooperation between various medical specialists, as well as the correct interpretation of additional tests, are essential for the accurate diagnosis. Each case of NF1 should not be belittled, and the occurrence of other conditions with symptoms similar to those of NF1 must always be considered.

It should be emphasized that, as in the described case, symptoms associated with potential NF1 complications and early signs of MS may give a similar clinical picture, thus delaying diagnosis of the latter. The first symptoms of MS in children are often associated with optic neuritis; therefore, ONGs-elated vision loss may cause omission of the first signs of MS. Given the relatively high prevalence of ONGs among patients with NF1, early diagnosis of MS and other causes of optic neuritis in such patients is difficult, thus additional tests should always be performed in any case of diagnostic uncertainty. However, even extensive differential tests, including ophthalmological consultation, imaging tests, electroretinography, and visual evoked potential tests, may not be conclusive; therefore, the careful neurological evaluation of patients with NF1 and visual deficit are necessary. This is particularly important as early recognition and treatment of MS in children can potentially result in significantly better outcomes.

The presented case report should be considered as an example of a multidisciplinary diagnostic approach towards NF1 patients with comorbidities, especially in patients with coexisting demyelinating syndromes. Managing such cases poses difficulties for clinicians because hitherto no guidelines have been developed. Case reports such as that presented are crucial for raising clinical awareness, and may contribute to the development of appropriate diagnostic criteria and treatment strategies in patients with NF1 and demyelinating diseases.

REFERENCES

1. Ly K, Blakeley J. The Diagnosis and Management of Neurofibromatosis Type 1. Med Clin North Am. 2019; 103(6): 1035–1054. https://doi.org/10.1016/j.mcna.2019.07.004
2. Crump T. Translation of case reports in Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen by F. v. Recklinghausen. Adv Neurol. 1981; 29: 259–275.
3. Antônio JR, Goloni-Bertollo EM, Trídico LA. Neurofibromatosis: chronological history and current issues. An Bras Dermatol. 2013; 88(3): 329–343. https://doi:10.1590/abd1806-4841.20132125
4. Messiaen LM. Molecular Diagnosis for NF1. In: Tadini G, Legius E, Brems H, editors. Multidisciplinary Approach to Neurofibromatosis Type 1. Cham: Springer International Publishing; 2020. p. 15–34.
5. Bergoug M, Doudeau M, Godin F, et al. Neurofibromin Structure, Functions and Regulation. Cells. 2020; 9(11): 2365. https://doi.org/10.3390/cells9112365
6. Kallionpää RA, Uusitalo E, Leppävirta J, et al. Prevalence of neurofibromatosis type 1 in the Finnish population. Genet Med. 2018; 20(9): 1082–1086. https://doi.org/10.1038/gim.2017.215
7. Uusitalo E, Leppävirta J, Koffert A, et al. Incidence and mortality of neurofibromatosis: a total population study in Finland. J Invest Dermatol. 2015; 135(3): 904–906. https://doi.org/10.1038/jid.2014.465
8. Neurofibromatosis: Conference Statement. Arch Neurol. 1988; 45(5): 575–578.
9. Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021. https://doi.org/10.1038/s41436-021-01170-5
10. Trevisson E, Cassina M, Opocher E, et al. Natural history of optic pathway gliomas in a cohort of unselected patients affected by Neurofibromatosis 1. J Neurooncol. 2017; 134(2): 279–287. https://doi.org/10.1007/s11060-017-2517-6
11. Sellmer L, Farschtschi S, Marangoni M, et al. Serial MRIs provide novel insight into natural history of optic pathway gliomas in patients with neurofibromatosis 1. Orphanet J Rare Dis. 2018; 13(1): 62. https://doi.org/10.1186/s13023-018-0811-9
12. Prada C, Hufnagel R, Hummel T, et al. The Use of Magnetic Resonance Imaging Screening for Optic Pathway Gliomas in Children with Neurofibromatosis Type 1. J Pediatr. 2015; 167(4): 851–856. https://doi.org/10.1016/j.jpeds.2015.07.001
13. Campen CJ, Gutmann DH. Optic Pathway Gliomas in Neurofibromatosis Type 1. J Child Neurol. 2018; 33(1): 73–81. https://doi.org/10.1177/0883073817739509
14. Multiple Sclerosis International Federation. Atlas of MS 2013: mapping multiple sclerosis around the world. Mult Scler Int Fed http://www.msif.org/about-us/advocacy/atlas/ (access: 2021.05.14).
15. Alroughani R, Boyko A. Pediatric multiple sclerosis: a review. BMC Neurol. 2018; 18(1): 27. https://doi.org/doi: 10.1186/s12883-018-1026-3
16. Madubata CC, Olsen MA, Stwalley DL, et al. Neurofibromatosis type 1 and chronic neurological conditions in the United States: an administrative claims analysis. Genet Med. 2015; 17(1): 36–42. https://doi.org/10.1038/gim.2014.70
17. Reinhardt K, Weiss S, Rosenbauer J, et al. Multiple sclerosis in children and adolescents: incidence and clinical picture – new insights from the nationwide German surveillance (2009–2011). Eur J Neurol. 2014; 21(4): 654–659. https://doi.org/10.1111/ene.12371
18. Suresh P, Kapoor R, Kapur BN. Severe neurotoxicity due to Vinblastine in Hodgkin lymphoma. South Asian J Cancer. 2014; 3(2): 147–148. https://doi.org/10.4103/2278-330X.130492
19. Boesen MS, Born AP, Jensen PEH, et al. Diagnostic Value of Oligoclonal Bands in Children: A Nationwide Population-Based Cohort Study. Pediatr Neurol. 2019; 97: 56–63. https://doi.org/10.1016/j.pediatrneurol.2019.03.002
20. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85(2): 177–189. https://doi.org/10.1212/WNL.0000000000001729
21. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013; 19(10): 1261–1267. https://doi.org/10.1177/1352458513484547
22. Etemadifar M, Fatehi F, Sahraian MA, et al. Multiple sclerosis and neurofibromatosis type 1: report of seven patients from Iran. Mult Scler. 2009; 15(9): 1126–1130. https://doi.org/10.1177/1352458509106612
23. Bergqvist C, Hemery F, Ferkal S, et al. Neurofibromatosis I and multiple sclerosis. Orphanet J Rare Dis. 2020; 15(1): 186. https://doi.org/10.1186/s13023-020-01463-z
24. Johnson MR, Ferner RE, Bobrow M, et al. Detailed analysis of the oligodendrocyte myelin glycoprotein gene in four patients with neurofibromatosis 1 and primary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2000; 68(5): 643–646. https://doi.org/10.1136/jnnp.68.5.643