ISSN 2082-369X

Przegląd Medyczny Uniwersytetu Rzeszowskiego
i Narodowego Instytutu Leków w Warszawie
Rzeszów 2013, 4, 501–508

Ewa Jamroz [1 (A,B,C,D,E,F,G)], Justyna Paprocka [1 (A,B,C,D,E,F,G)], Jerzy Pietruszewski [1 (A,B,C,D,E,F,G)], Anna Bojda [2 (B,D,G)], Alicja Betkiewicz [2 (B,D,G)]

Multiple sclerosis in children – clinical aspects and diagnostic dilemmas

Stwardnienie rozsiane u dzieci – aspekty kliniczne i dylematy diagnostyczne

[1] Klinika Pediatrii i Neurologii Wieku Rozwojowego, Śląski Uniwersytet Medyczny, Katowice
[2] Studenckie Towarzystwo Naukowe przy Klinice Pediatrii i Neurologii Wieku Rozwojowego Śląskiego Uniwersytetu Medycznego, Katowice

ABSTRACT

Background. Multiple sclerosis (MS) is a chronic, acquired demyelinating disease affecting central nervous system. The pathogenesis of the disorder is still unclear, although experimental models provide evidences of autoimmune and inflammatory basis of the disease. The estimated occurence of MS is 3.6 cases per 100,000 person-years in women and 2.0 in men. Up to 10% of patients experiences their first symptoms before the age of 18. The diagnosis of MS in adults is based on Mc Donald criteria, that include clinical symptoms, magnetic resonance imaging (MRI) of the brain and spinal cord, the presence of oligoclonal bands in cerebrospinal fluid (CSF) and abnormal visual evoked potentials. These criteria are less useful in early stages of the disease in children. The exact diagnosis in young patients is even more difficult because of clinical presentation which may suggest other inflammatory-demyelinating and neurometabolic diseases.
Aim. The authors analyze a group of 29 children (clinical presentation and additional examinations) in reference to current diagnostic criteria.

STRESZCZENIE

Wstęp. Stwardnienie rozsiane (SM) jest przewlekłą, nabytą chorobą demielinizacyjną ośrodkowego układu nerwowego. Patogeneza choroby nadal pozostaje nieznana, chociaż modele eksperymentalne dostarczają dowodów na temat podłoża zapalno-demielinizacyjnego. Szacowana częstość występowania SM wynosi 3.6 przypadków na 100 000 osobolat wśród kobiet oraz 2.0 u mężczyzn. Około 10% chorych doświadcza pierwszych objawów przed 18. rokiem życia. Diagnoza SM u osób dorosłych opiera się na kryteriach McDonalda, które obejmują objawy kliniczne, ocenę zmian w badaniach neuroobrazowych (MR głowy i rdzenia kręgowego), obecność prążków oligoklonalnych w płynie mózgowo-rdzeniowym oraz nieprawidłowe potencjały wywołane. Te kryteria są mniej przydatne w populacji dziecięcej, we wczesnych stadiach choroby. Postawienie prawidłowej diagnozy u młodszych pacjentów stanowi problem diagnostyczny, ponieważ objawy kliniczne mogą sugerować inną chorobę zapalno-demielinizacyjną lub neurometaboliczną.
Cel pracy. Celem pracy była retrospektywna analiza obrazu klinicznego oraz wyników badań dodatkowych u dzieci z

Udział współautorów / Participation of co-authors: A. autor koncepcji i założeń pracy / author of the concept and objectives of paper; B. zbieranie materiału / collection of data; C. realizacja badań / implementation of research; D. opracowanie, analiza i interpretacja wyników / elaborate, analysis and interpretation of data; E. analiza statystyczna danych / statistical analysis; F. przygotowanie manuskryptu / preparation of a manuscript; G. opracowanie piśmiennictwa / working out the literature; H. pozyskanie funduszy / obtaining funds

Artykuł otrzymano / recived: 7.03.2013 | Zaakceptowano do publikacji / accepted: 14.09.2013

Material and methods. The analyzed group consisted of 27 children hospitalized in Child Neurology Department of Medical University of Silesia in Katowice in the years 2005-2010. The average age at diagnosis was 15 years, the range was 5 to 17 years.

Results. All children exhibited relapsing, remitting multiple sclerosis. In the analyzed group, patients presented with initial symptoms concerning predominantly sensory and motor symptoms - 52 %. The oligoclonal bands were present in 91% of examined children. 58% of patients fulfill the 2005 McDonald criteria, revised 2010 McDonald criteria 90%. 17 children presented three out of four Barkhof magnetic resonance imaging criteria.

Key words: multiple sclerosis, children, diagnostics

rozpoznanym stwardnieniem rozsianym w odniesieniu do aktualnie obowiązujących kryteriów.

Materiał i metody. Grupę badaną stanowiło 29 dzieci w wieku od 5 do 17 lat (wiek średni: 15lat) hospitalizowanych w Klinice Pediatrii i Neurologii Wieku Rozwojowego SUM w Katowicach w latach 2005–2010.

Wyniki. U wszystkich dzieci rozpoznano postać rzutowo-remisyjną stwardnienia rozsianego. Najczęściej występującymi pierwszymi objawami były zaburzenia ruchowe i czuciowe (52%). U 91% dzieci stwierdzono obecność prążków oligoklonalnych. 58% pacjentów spełniało kryteria McDonalda z 2005 r., 90% – kryteria McDonalda z 2010 r., natomiast 17%pacjentów 3 z 4 kryteriów Barkhofa.

Słowa kluczowe: stwardnienie rozsiane, dzieci, diagnostyka

Praca powstała w ramach pracy statutowej: „Kompleksowa diagnostyka stwardnienia rozsianego" KNW-1-132/P/1/0

Introduction

Multiple sclerosis is one of the most frequent diseases affecting nervous system in young adults, especially in the third decade of life. After trauma it is the second neurologic cause of disability in the age group mentioned above. With the development of diagnostic methods, the number of cases diagnosed in children aged 17 or younger rises significantly worldwide. According to the estimations, up to 10% of all patients with MS have the diagnosis established before the age of 18 and 3–5% of all individuals with MS experience the onset of their disease prior to age 16 [1, 2]. These data may be however imprecise because some reports, include also patients diagnosed above 18 years, but experiencing their first symptoms before that age. For the purposes of this study the term 'pediatric multiple sclerosis' is used in reference to all patients diagnosed prior to the 18th birthday, following the criteria used by International Pediatric MS Study Group. MS in children under the age of 10 (referred to as 'pediatric multiple sclerosis' by the World Health Organization) is very rare making an estimated 0,2% to 0,7% of all MS patients [3, 4]. Children (<15years) moving from a country of low multiple sclerosis risk to a country of high multiple sclerosis risk acquire the high MS risk of a new country [4, 5]. Over 75% of children with MS will experience their second attack within the first year.

The majority of children have a relapsing-remitting MS course with 1–1,9 relapses per year in the first few years of disease which may be higher than in adult-onset MS [1–5]. Approximately one-third of children demonstrate worsening of cognitive function early in the disease course in contrast with slower disability progression assessed by the Expanded Disability Status Scale. According to Armato et al 75% had cognitive deficits on follow-up at two years [6].

There are unceasing discussions on the causes of multiple sclerosis, and the precise etiology is still unknown, although epidemiological research point to infections ("molecular mimicry" to myelin antigens: myelin basic protein, myelin oligodendrocyte glycoprotein, proteolipid protein) as probably important factor in the development of MS [4]. The recent data suggest the increased frequency of Ebstein virus seropositivity with MS susceptibility in pediatric population. Also protective role of remote infection with Herpes simplex or cytomegalovirus was postulated. Apart from environmental factors (infectious exposures and vitamin D status) a complex genetic background may contribute to the disease manifestation. Patients with HLA-DR2 (DR1501) haplotype, precisely HLA-DRB5*01101-HLADRB11501-HLA-DQA1*0102-HLA-DQB1*0602 and single –nucleotide polymorphism of IL-2R and IL-7R alleles have increased risk for MS development [1–5]. The knowledge on pathogenesis of MS increased significantly in the last years. The nervous system lesions in the course of disease are the result of mainly two processes, first of which is oligodendrocyte damage and demyelination (in a predominantly perivascular pattern), totally or at least partially reversible [4, 5]. The second process, strongly emphasized in recent years, axonal loss, responsible for progressing, irreversible degeneration also in the normal appearing white matter tracts and is related to functional disability and disease progression.

Autoimmune processes leading to nervous system damages are mediated by wide range of immune cells, predominantly by the T cells (CD4+T cells and probably $T_H1$and T_H17), but also others like B cells or macrophages [5, 7]. There are some areas of the brain that are particularly prone to lesions in MS, including optic nerves, brain stem, cerebellum and spinal cord, but every white matter structure may possibly be affected by the disease [5, 8]. It determines that there is no characteristic constellation of symptoms for multiple sclerosis. It is worth mentioning that there are also evidences of gray matter loss as well as white matter – especially cortical and thalamic gray matter [9].

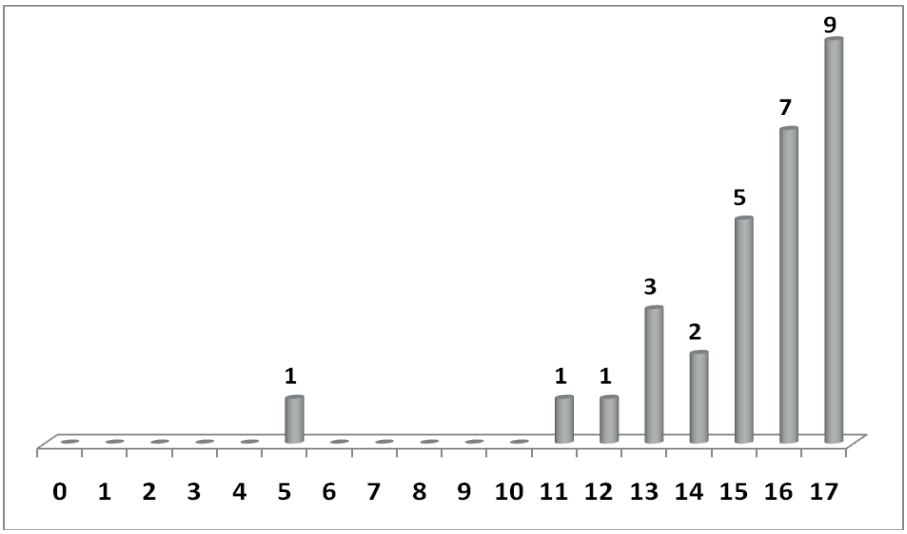

Fig. 1. Age of patients at the time of diagnosis

Clinical criteria for diagnosing MS require relapses persist for a minimum of 24 hours, the disease attacks should be separated more than 30 days. MRI confirmed a dissemination of disease in space (DIS) and in time (DIT). The 2010 McDonalds (prior diagnostic algorithm proposed in 2001 and 2005) criteria can be fulfilled if the patient experienced two or more relapses DIT or DIS irrespective of MRI features. According to a cohort study of MS pediatric patients by Sadaka et al, these criteria are not suitable for children with ADEM- like presentation and for children under 11years.

In some cases clinical presentation (clinical evidences for two or more relapses or clinical symptoms correlated with the MR presentation) are sufficient to establish the diagnosis of MS [10–15]. In other cases there is a need for CSF examination and/ or evoked potentials. First of mentioned tests is able to prove intrathecal synthesis of immunoglobulins [16]. According to the literature, oligoclonal bands are present in more than 95% of adult patients with MS, but are not specific for the disease, as they can occur in many other conditions like neoplastic disorders or infections [16]. The lesions of white matter not always result immediately in visible symptoms. The analysis of visual, sensory and brain stem evoked potentials that can show of nerve conduction in particular white matter tracts is therefore a valuable diagnostic test in multiple sclerosis.

Material and methods

The authors analyze a group of 29 children hospitalized in Child Neurology Department in Katowice in the years 2005–2010 in reference to current diagnostic criteria. Within the analyzed group of 27 children, average age at diagnosis was 15 years, the range was 5 to 17 years (Fig. 1). 33% of patients were diagnosed at the age of 17 and only one child, a five years old girl, was diagnosed before the age of 10.

All parents and children above 16 years signed informed consent for lumbar puncture. A total of 5 ml of cerebrospinal fluid was collected in glass tubes (via lumbar puncture using an atraumatic needle) and 10ml of blood were drawn from each patient. Within 30 min of collection, the CFS was centrifuged and both serum and CSF were deep frozen (–20°C) until analysis. The albumin and IgG in serum and CSF were determined in a certificated laboratory with commercially available kits. The albumin quotient (CSF albumin/serum albumin) was used as a measure of blood-brain barier (BBB) integrity in conjuction with the IgG quotient (CSF IgG/ serum IgG). The IgG index (IgG quotient/ albumin quotient) was used for determination of intrathecal synthesis. An IgG index value of >0,7 was taken to indicate the presence of intrathecal synthesis. The examination of oligoclonal bands was performed using isoelectric focusing on agarose gels.

The Kurtzke Expanded Diaability Status Scale (EDSS) was determined for all patients before the lumbar puncture procedure.

All magnetic resonance imaging scans were accessed by revised 2010 McDonald criteria as well as fulfillment of at least three out of four Barkhof criteria. There are as follow:

1. at least nine lesions on the T2-weighted images,
2. the presence of at least three periventricular lesions,
3. the presence of at least one juxtacortical lesion,
4. the presence of at least one infratentorial lesion.

During the brain MRI analysis we also scored the presence of lesions in the thalamus and basal ganglia and white matter lesions perpendicular to the corpus callosum and the sole presence of well-defined lesions (KIDMUS criteria).

Results

Clinical presentation: All children exhibited relapsing-remitting multiple sclerosis.

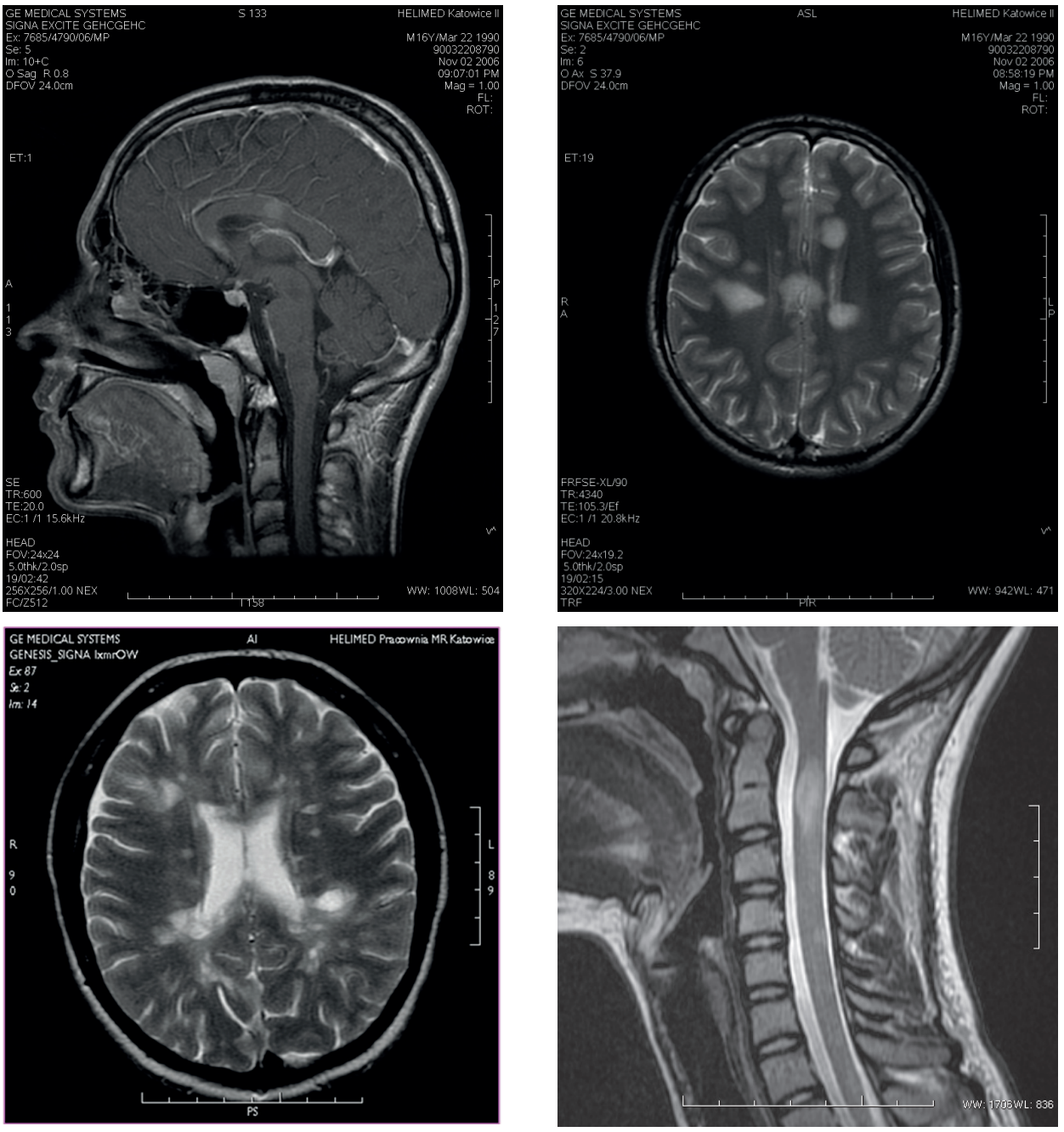

Fig. 2–5. MRI features in MS

In the analyzed group, patients presented with following initial symptoms:

— sensory and motor disorders – 52 %
— cerebellar and brain stem symptoms – 24%
— optic neuritis – 17%
— polysymptomatic – 7%.

Sensory disorders included mainly numbness usually with dysesthesia. In some cases hypoestesia occurred. Impairment of motor functions included mainly pyramidal symptoms. As to cerebellar and brain stem symptoms, nystagmus and vertigo were most frequent. None of the patients experienced bladder of bowel dysfunction as the initial symptom, but two of them presented that symptoms in course of the disease. In one case the only initial symptom was a headache. With progression of the disease most of described patients became polysymptomatic. Abnormalities in neuropsychological tests were visible in near all patients.

Evoked potentials: Visual evoked potentials (VEPs) – were examined in 24 of 29 patients and among examined abnormal potentials were observed in 71% of patients (also when there were no clinical evidences of optic neuritis) which is consistent with the data of adult patients /abnormalities in 70% of patients. 22 of all patients had also sensory evoked potentials (SEPs) and 23 brain stem auditory evoked potentials (BAEPs) examined and abnormalities occured in 32% of SEPs and only 9% of BAEPs.

CSF examination: Cerebrospinal fluid examination was performed in all patients. The oligoclonal bands were present in 91% of examined children. Among those, who had oligoclonal bands present in CSF, the IgG index was elevated in 48% of cases.

MRI features (Fig. 2–5): MR of the brain and spinal cord has shown demyelinating lesions in all patients. 58% of patients fulfill the 2005 McDonald criteria, revised 2010 McDonald criteria 90%. 17 children presented three out of four Barkhof magnetic resonance imaging criteria.

Treatment: In management of acute MS relapses intravenous methylprednisolone 10–30 mg/kg for 3–5 days was introduced. None of the patients received immunoglobulins or plasma exchange. None of the children were treated with interferon because such treatment was not achived that time.

Discussion

Many attempts have been made recently in order to create diagnostic criteria, directed to the paediatric patients, that will enable clinicians to establish quick and accurate diagnosis. This is particularly important, as there is increasing number of the reports on positive effects of disease modifying therapy in children younger than 16 years [17]. Many reports show advantages of early initiation of disease modifying treatment in adults. On the other hand, each therapy having so significant impact on still developing child`s immune system has to be to given a very careful consideration. The international consensus on disease severity and magnetic resonance criteria may help also to identify children with high risk of an early relapse. In MS immune mediated myelin loss is accompanied by variable degree of axonal injury [13, 18, 19].

Despite advance in diagnostic methods, multiple sclerosis in children is still undoubtedly a great diagnostic dilemma, regarding a number of infectious and neurometabolic diseases which can mimic the symptoms as well as MRI presentation. The first to be mentioned is acute disseminated encephalomyelitis (ADEM) [20, 21]. ADEM and MS can be undistinguishable at the time of first presentation and 5 to 18% of such children will ultimately be diagnosed with MS [20]. ADEM typically has a monophasic course with favorable prognosis. By definition proposed by the International Multiple Sclerosis Study Group ADEM patients present with multifocal central nervous system involvement and encephalopathy (Fig. 6–7) [20, 21]. The mean age at first symptoms (subacute or acute onset usually from 2 days to 4 weeks following a viral infection) ranges from 5 to 8 years. The neurologic symptoms in ADEM comprise: unilateral or bilateral pyramidal signs (60-95%), acute hemiplegia (76%), ataxia (18–65%), cranial nerve palsies (22–45%), visual loss due to optic neuritis (7–23%), seizures (13–35%), spinal cord involvement (24%), impairment of speech (5–21%), hemiparesthesia (2–3%) with alteration in consciousness varying from lethargy to coma [2, 20–22]. Acute disseminated encephalomyelitis was reported in 22% to 29% of children who presented with acquired demyelinating syndromes [20, 21]. There are risk factors for relapse and subsequent diagnosis of MS are presented in table 1.

D-Alessandro et al performed study showing the rate of conversion from clinically isolated syndromes (CIS) to MS [18]. Univariate analysis proved that age, number of FS (Kurtzke Functional Systems) involved at onset, number of gadolinium enhancement lesions, positive Barkhof criteria and intravenous steroid treatment

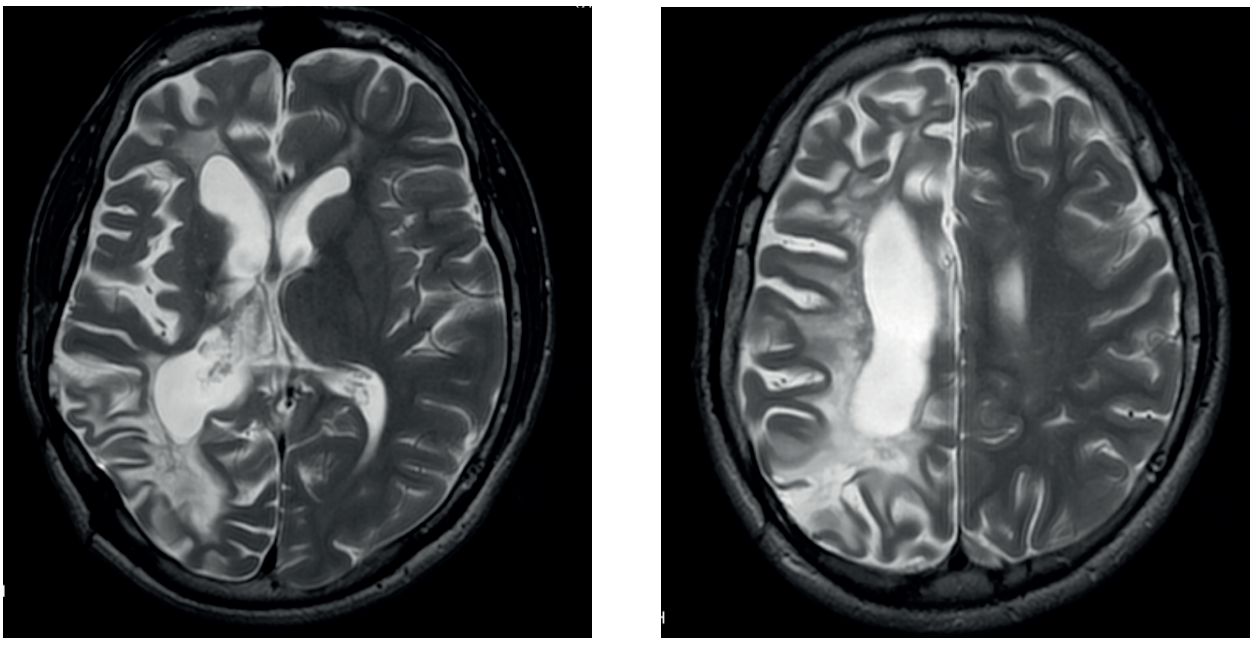

Fig. 6–7. ADEM MRI features

Tab. 1. Risk factors for multiple sclerosis following acute demyelination according to Alper G et al. [2, 18]

Increased risk	Decreased risk
Greater than 10 years of age No encephalopathy No precipitating infection Optic neuritis Intrathecal oligoclonal bands Family history of MS Periventricular perpendicular ovoid lesions (Dawson figures)	Less than 10 years Encephalopathy Postinfectious presentation Isolated transverse myelitis Meningismus, fever or seizures

Tab. 2. Differential diagnosis of MS in children according to Banwell et al. [2]

Inflammatory diseases	ADEM, neuromyelitis optica (NMO), neuroboreliosis, tuberculosis, syphilis, Creutzfeld-Jacob disease (vCJD), infection with HSV5, HCV, Mycoplasma pneumoniae, periventricular leukomalacia, Whipple disease
Neurometabolic diseases	X-adrenoleukodystrophy, metachromatic leukodystrophy, globoid leukodystrophy, Fabry disease, mitochondrial encephalomyopathy, Wilson disease, Pelizaus-Merzbacher disease, Canavan disease, Alexander disease, van Bogaert disease, abetalipoprotein deficiency
Vascular abnormalities	CADASIL, antyphospholipid syndrome, Binswanger disease, migraine, vascular malformation of the brain vessels
Neurodegenerative diseases	amyotrophic lateral sclerosis, hereditary spastic paraplegia, spinocerebellar ataxias, Friedreich ataxia
Connective tissue disorders	systemic lupus, mixed connective tissue, scleroderma, Sjogren disease, Behcet disease
Tumors	lymphomas, leukemia, axial located tumors

were predictive of conversion to MS. The differential diagnosis include also neuroboreliosis, vascular disorders and some inborn diseases like leukodystrophies (table 2, see Fig. 8) [20, 21]. In about 10% of patients infected with Borrelia burgdorferi have neurological symptoms typical for second stage of infection [21]. In some most problematic cases neuroboreliosis may manifest with transverse myelitis, ataxia, chorea or peripheral neuritis of remitting relapsing course. That is why exclusion of borreliosis by determination of antibodies against borrelia burgdorferi should be always indicated.

Most of the leukodystrophies are easily differentiated from SM as they present with a chronic progressive course characterized with neurologic deterioration and development regression. MRI usually shows diffuse symmetric white matter lesions (Fig. 8–9) [5, 8, 11, 20, 21]. Vanishing white matter disease like ADEM may demonstrate episodic worsening following infection or trauma. Althought MRI is useful in considering diagnosis it could be limiting, as different genetic disorders may share comparable patterns of cerebral involvement.

For many years cerebrospinal fluid sample, including cellular content, oligoclonal bands and IgG index is very important for diagnosing MS [5, 8, 11]. Especially in adults, an elevated IgG index or the presence of cerebrospinal fluid – restricted IgG oligoclonal bands are included in the diagnostic criteria [7]. The percentage of pediatric patients with oligoclonal bands (64–92%), an elevated IgG index (64–75%), pleocytosis (33–73%) [7, 22, 23]. MS younger children are more likely to be oligoclonal band negative, the same age-related immature answer of the immune system is seen with IgG index elevation [23].

In the analyzed group 90% of patients met the 2010 McDonald criteria for lesions dissemination in space (at initial demyelinating event). In the studied group MRI lesions were generally located in the periventricular and subcortical white matter [15]. According to the literature only 67% of children met adult 2005 MS McDonalds criteria [9, 11, 13–15]. According to Neuteboom et al. the presence of at least three positive Barkhof criteria in children is a prognostic factor for early relapse after a diagnosis of multiple sclerosis [14]. The sensitivity of KIDMUS criteria was found to be poor, especially in children younger than 10 years [9, 11, 13]. The McDonald criteria were revised again in 2010 and they simplified MRI requirements and according to Sadaka et al are suitable for the diagnosis of pediatric MS [15].

According to the recommendation of MS treatment all children received methylprednisolone for acute MS relapses [24-17]. None of the patients was treated with intravenous immunoglobulin. A small number of case report of children receiving immunoglobulin in optic neuritis and acute disseminated encephalomyelitis or relapses poorly respond to corticosteroids have been published [17–24]. Plasma exchange in cases of fulminant demyelination has according to American Academy of Neurology guidelines, a level of B recommendation as a second-line therapy in adult relapses [24]. Disease-modifying therapies that may prevent relapses comprise 4 injectables therapies: interferon β-1a(INFβ-1a)

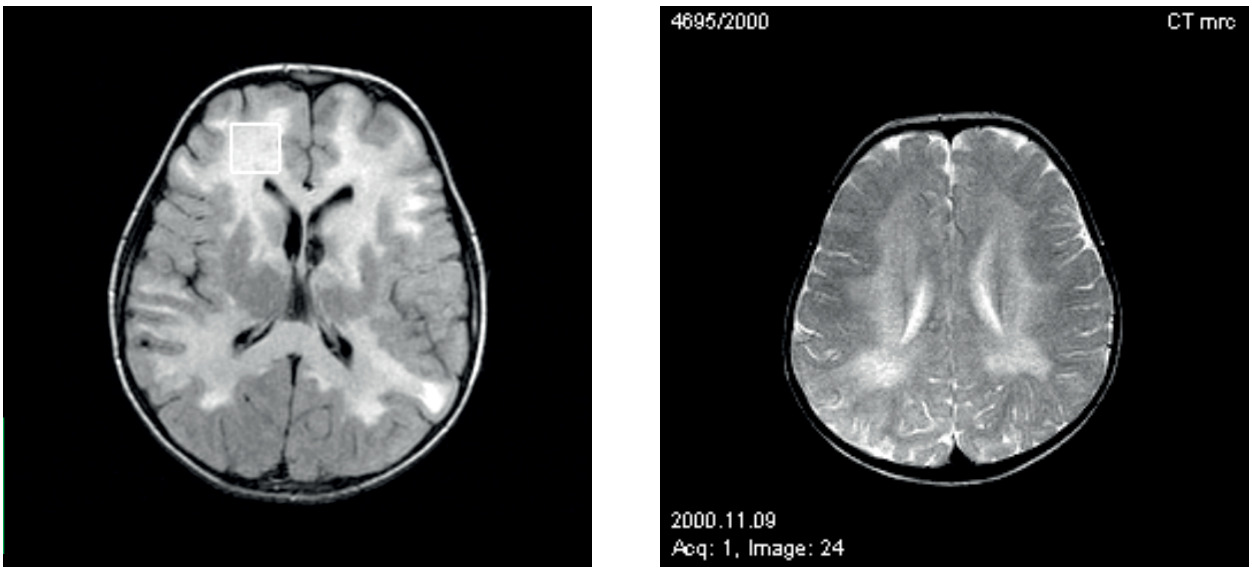

Fig. 8–9. MRI scan of patient with X-ALD (left) in comparison to MRI presentation of a patient diagnosed with metachromatic leukodystrophy (right)

intramuscular (once a week), interferon β-1a subcutaneous (3 times a week), interferon β-1b subcutaneous (every other day) and glatiramer acetate subcutaneous (daily). Dosing of interferon β is not established in pediatric population [24–17]. European and International Pediatric Multiple Sclerosis Study Group suggest a titration according to adult protocol or gradual titration to 30 μg once weekly for intramuscular injection interferon β-1a and 22μg 3 times weekly or 44 μg 3 times weekly for subcutaneous interferon β-1a, and 250 μg for interferon β-1b [24]. Limited data on second-line therapies, including natalizumab, daclizumab and cyclophosphamide based on open label studies in children and adolescents suggest possible efficacy and maybe tolerance but still significant risk for side effects exist [24–26].

Identification of immune and inflammatory pathology, which is the most probable in MS, may help to identify the targets for therapeutics. Due to high frequency of relapses and possibility of disability at young age early diagnosis and treatment in children is very important.

Piśmiennictwo / References

1. Krupp L, Banwell B, Tenembaum S, for the International Pediatric MS Study Group. *Consensus definitions proposed for pediatric multiple sclerosis*. Neurology 2007;68: S7–S12.
2. Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. *Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions*. Lancet Neurol 2007;6: 887–902.
3. Alonso A, Hernan M. *Temporal trends in the incidence of multiple sclerosis: a systematic review*. Neurology 2008; 71: 129–135.
4. Vargas-Lowy D, Chitnis T. *Pathogenesis of pediatric multiple sclerosis*. J Child Neurol 2012;27:1394-1407.
5. Bigi S, Banwell B. *Pediatric Multiple Sclerosis*. J Child Neurol 2012;27:1378-1383.
6. Armato MP, Goretti B, Ghezzi A et al. *Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up*. Neurology 2010;75:1134-1140.
7. Tumani H, Hartung HP, Hemmer B et al. *The BioMS Study Group. Cerebrospinal fluid biomarkers in multiple sclerosis*. Neurobiol Dis 2009;35:117-127.
8. Huppke P, Gartner J. *A practical guide to pediatric multiple sclerosis*. Neuropediatrics 2010;41;157-162.
9. Mesaros S, Rocca MA, Absinta M et al. *Evidence of thalamic grey matter loss in paediatric multiple sclerosis*. Neurology 2008;70:1107–12.
10. Ness J, Chabas D, Sadovnick A, Pohl D, Banwell B, Weinstock-Guttman B. *Clinical features of children and adolescents with multiple sclerosis*. Neurology 2007;68;S37--S45.
11. Callen D, Shroff M, Branson H, Lotze D, Li D, Stephens D, Banwell B. *MRI in the diagnosis of pediatric multiple sclerosis*. Neurology 2009;72:961-967.
12. Sobocki P, Pugliatti M, Lauer K, Kobelt G. *Estimation of the cost of MS in Europe: extrapolations from a multinational cost study*. Multiple Sclerosis 2007;13:1054-64.
13. Banwell B, Shroff M, Ness JM, Jeffery D, Schwid S, Weinstock-Guttman B. *MRI features of pediatric multiple sclerosis*. Neurology 2007;68 (suppl 2):S46–S53.
14. Neuteboom RF, Ketelslegers IA, Boon M et al. *Barkhof magnetic resonance imaging criteria predict early relapse in pediatric multiple sclerosis*. Pediatr Neurol 2010;42:53-5.
15. Sadaka Y, Verhey LH, Shroff M et al on behalf of the Canadian Pediatric Demyelinating Disease Network. *2010 Mc Donald Criteria for diagnosing pediatric multiple sclerosis*. Ann Neurol 2012;72:211-223.

16. Link H, Huang YM. *Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness*. J Neuroimmunology 2006; 180: 17–28.
17. Chitnis T. *Disease-modifying therapy of pediatric multiple sclerosis*. Neurotherapeutics 2013;10:89-96.
18. D'Alessandro R, Vignatelli L, Lugaresi A et al. *Risk of multiple sclerosis following clinically isolated syndrome: a 4-year prospective study*. J Neurol 2013; 10.1007/s00415-013-6838-x
19. Bolcaen J, Acou M, Mertens K et al. *Structural and metabolic features of two different variants of multiple sclerosis: a PET/MRI study*. J Neuroimaging 2012;XX:1-6.
20. Eckstein C, Saidha S, Levy M. *A differential diagnosis of central nervous demyelination: beyond multiple sclerosis*. J Neurol 2012;259:801-816.
21. Absound M, Wassmer E. *Childhood CNS inflammatory demyelinating diseases*. Pediatr Child Health 2010;20:404-410.
22. Mayringer I, Timeltaler B, Deisenhammer F. *Correlation between the IgG index, oligoclonal bands in CSF, and the diagnosis of demyelinating diseases*. Eur J Neur 2005; 12:527-530.
23. Mitosek-Szewczyk K, Gordon-Krajcer W, Flis D, Stelmasiak Z. *Some markers of neuronal damage in cerebrospinal fluid of multiple sclerosis patients in relapse*. Folia Neuropathol 2011;49:191-196.
24. Ghezzi A, Banwell B, Boyko A et al. *The management of multiple sclerosis in children: A European view*. Multiple sclerosis 2010;16:1258-1267.
25. Yeh EA, Weinstock- Guttman B. *The management of pediatric multiple sclerosis*. J Child Neurol 2012;27:1384-1393.
26. Chitnis T, Tenembaum S, Banwell B et al and for the International Pediatric Multiple Sclerosis Study Group. *Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis*. MSJ 2012; 18:116-127.
27. Pohl D, Waubant E, Banwell B et al. *Treatment of pediatric multiple sclerosis and variants*. Neurology, 2007; 68: S54 - S65.

Adres do korespondencji / Mailing address:
Ewa Jamroz
Klinika Pediatrii i Neurologii Wieku Rozwojowego SUM,
ul. Medyków 16, 40-752 Katowice
e-mail: ejamroz@sum.edu.pl