Natalizumab in the treatment of pediatric multiple sclerosis

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Abstract

Pediatric cerebrospinal multiple sclerosis (MS) constitutes about 2–5% of all MS cases. The International Pediatric MS Study Group (IPMSSG) applies diagnostic criteria for adults to MS in childhood and adolescence. Recent publications highlight an increasing number of MS in children resistant to the first-line treatment, i.e. disease modifying therapy (DMT). Furthermore, the number of published case studies on children with highly active MS treated with natalizumab also rises, whereas long-term risks as well as therapeutic potential of this therapy in pediatric population have been at the centre of attention. This paper presents a group of 5 children in whom natalizumab was selected to manage highly active disease or resistance to conventional MS treatment and provided very good clinical as well as MRI results.

INTRODUCTION

Although MS may occur in childhood, no specific characteristics have been identified for this patient population. Pediatric forms of MS are most frequently classified according to the age of onset as defined by Bauer (1989) and Hanefeld (1993) into three groups:

- Early infantile MS (EIMS) with an onset between 1–5 years of age
- Delayed infantile MS (DIMS) with an onset between 5–10 years of age
- Juvenile MS (JMS) with an onset between 10–16 years of age.

MS prevalence and incidence in childhood and adolescence has not been fully established yet but it had been estimated at 2.7% to 5.6% of all MS patients. The juvenile form is more frequent than the infantile form. While living in the northern latitudes before 15 years of age is associated with an increased risk of the disease, early immigration (before 15 years of age) to the south reduces the risk. Besides latitude, exposure to certain viral groups, particularly the Epstein-Barr virus (EBV), vitamin D level and smoking status are other environmental risk factors that apply to children. Children who have had infectious mononucleosis have up to 17 times higher risk of developing MS. Besides this viral exposure, increased use of vaccines over the recent years, particularly against hepatitis B, shown to be associated with subsequent MS development, might play a role. However, a study of a French pediatric population revealed no increase in postvaccination risk of the first MS attack up to 3 years of age (Mikaeloff *et al.* 2007; Mikaeloff *et al.* 2009), although this risk might increase with time. Studies found no increased risk of relapses in connection to vaccination against hepatitis B and tetanus in children after the first MS attack. The recent introduction of vaccination of adolescent girls against human papillomavirus infections poses a question whether vaccinations are associ-

CASE REPORT

ated with an increased risk of MS in specific populations, such as adolescent girls. Continuous exposure of the population to vaccination might have resulted in a random time correlation between vaccination and the first episode of CNS demyelination. The same group of children with MS was involved in a study investigating a relationship between MS or its relapse and exposure to passive smoking (Mikaeloff *et al.* 2007); two times higher passive smoking rate was found in children with MS compared to those with non-smoking parents. This risk of MS rose further with exposure time of 10 years and more (Mikaeloff *et al.* 2007). In adults, higher susceptibility to the development of MS is assumed in individuals with lower vitamin D level. Even though children have generally lower levels of 25-hydroxyvitamin D3 than adults, a similar relationship between lower vitamin D levels and MS was also confirmed in children with MS. It has been generally accepted that the development of MS depends on genetic predisposition in connection to one or more environmental risk factors that may "trigger" the disease.

MS in childhood is also understood as a primary inflammatory demyelinating disease of the CNS. Epidemiological data indicate a probably more important effect of environmental factors, as partially documented by MS distribution, i.e. areas with high or low risk of occurrence. This is evidenced by isolation of viral proteins and genomic material from the brain tissue of children with MS. Besides EBV, herpes virus type 6, paramyxovirus and retrovirus are also among the viruses probably related to MS. Extracellular particles of the recently identified human endogenous retrovirus (HERV)-W have been associated with MS (Multiple Sclerosis-Associated Retrovirus, MSRV). MSRV identified in cerebrospinal fluid (CSF) corresponds to the level of CNS inflammation and could be used as a prognostic marker of an early phase MS in childhood. It has been generally accepted that an early viral infection may cause an autoimmune reaction with myelin antigens; this reactivity spreads in time to other myelin epitopes, leading to the development of clinical MS. The mechanism of this process seems to be similar, irrespective of age. After penetrating the hematoencephalic barrier (HEB), CD4+ T cells activated in the periphery find their specific receptors in the CNS in the context of MHC class II molecules expression by local antigen-presenting cells and dendritic cells. Class Th1 cells are activated, causing myelin disruption and a release of new potential CNS autoantigens. CD8+ cells also expand to MS plaques, causing acute axonal loss to a much higher extent than CD4+ (Neumann, 2003). Tissue destruction is catalyzed by concurrent secretion of pro-inflammatory cytokines (IFN-gamma, TNF-alpha), chemokines together with other non-specific inflammatory cells and specific antimyelin antibodies from B cells (Neumann, 2003). The inflammatory cascade with axonal demyelination at its top depends on peripheral T lymphocyte activation. Adhesion molecules play a key role in the lymphocyte transfer through HEB. These are intercellular adhesion molecules-1 (ICAM-1), glycoproteins reacting with alpha-2 integrins. Other adhesion molecules that facilitate interactions between lymphocytes and endothelial cells, as well as occurrence of perivascular infiltrate, include vascular cellular adhesion molecules-1 (VCAM-1), L-selectin and E-selectin (Masterman *et al.* 2000). This is where natalizumab exerts its effect.

Therapeutic approaches to ameliorate MS are based on this pathogenic knowledge and entails much more than merely a management of an acute attack, or relapse, with corticosteroids. Clinical relapses occur much less frequently than new inflammatory lesions shown on cerebral and spinal MRI scans. The need for long-term therapy was partially satisfied with an introduction of biological treatment with interferon-β (IFN-β) and glatiramer acetate (GA) in the 1990, the efficacy of which was verified in clinical studies with relapsing-remitting MS patients. The number of acute clinical relapses was reduced by approximately 30%, reducing disability progression and the number of active lesions visible on MRI scans (Havrdova, 2007).

There is growing evidence that MS treatment approved by FDA for adults (over 18 years of age), called the first-line therapy with disease modifying drugs (DMD) – interferon-β (IFN-β) or glatiramer acetate (GA), is also well tolerated in children with MS (Ghezzi *et al.* 2009; Banwell *et al.* 2006; Mikaeloff *et al.* 2008). At least 1/3 of children with MS develop moderate or rather severe disability and an onset of secondary progression comes at a younger age than in adults; several relapses during the first few years of the disease is a negative prognostic factor, and a high percentage of children with MS develop cognitive dysfunction. The use of a therapy that has a favourable effect on, if possible, all these acute or long-term aspects of the disease is thus justified. Similar to adults, the efficacy of this therapy is limited in terms of relapse reduction, slower disability progression and reduction in the number and volume of lesions shown on magnetic resonance imaging (MRI) scans. In retrospective studies, a number of children on this therapy show reduced tolerance with approximately 1/5 of children having to discontinue their treatment with IFN-β or GA. This therapy shows insufficient efficacy in about 1/4 of children and switching the therapy may have a crucial effect on the further course of the disease, whether it is chemotherapy or treatment with natalizumab, daclizumab, rituximab, mitoxantron, mycophenolate mofetil, or steroid pulses or intravenous immunoglobulins.

Recent publications draw attention to the rising number of children with MS resistant to the first-line treatment, i.e. disease modifying therapy (DMT). There are a rising number of published pediatric cases with highly active MS who were treated with natalizumab; the authors discuss long-term risks and benefits of this therapy in the pediatric population.

Natalizumab is a specific recombinant humanized monoclonal antibody against alpha-4 integrins. As for its fundamental mechanism of action, natalizumab enters into interaction with alpha-4 integrins, specifically with the alpha4-β1, alpha4-β7 integrins on lymphocytes and their ligands, adhesion molecules VCAM-1 and MAdCAM-1. It prevents the alpha4-β1 and alpha4-β7 from binding to their endothelial binding receptors VCAM-1 and MAdCAM-1. By binding to adhesion molecules on lymphocytes, natalizumab restricts lymphocyte entry into CNS and leads to considerable reduction of the inflammation. Clinical studies have indicated the capacity of natalizumab to reduce relapse rate by 68% compared to placebo, to reduce disability progression by 42% compared to placebo, to reduce the number of gadolinium (Gd) enhancing lesions by 92%, to reduce the number of new or enlarging T2 hyperintense lesions by 83% in the second year of therapy and to reduce T1-hypointense lesions by 76%. Currently, natalizumab is considered to be the most effective agent in MS therapy (Havrdova, 2010; Kappos *et al.* 2011).

CASE REPORTS

This paper presents case reports of 5 children (3 girls and 2 boys), aged 9–16 years at the onset of their neurological symptoms. The cases include 1 child with delayed infantile MS (DIMS) with onset at 9 years of age, the remaining 4 cases represent juvenile MS (JMS) with onset at 12–16 years of age. In 3 of the 4 JMS cases, natalizumab was initiated at 16–17 years of age as MS treatment escalation due to insufficient efficacy and intolerance of the first-line MS therapy – DMD or a combined immunomodulatory and immunosuppresive DMD therapy. In the single DIMS case and in one JMS case, natalizumab therapy was the primary choice due to a development of extensive cerebral and spinal white matter impairment at 13 and 17 years of age, respectively. The "Stratify JCV test" to determine anti-JCV antibodies was performed in all children when it became available in 2011 and was negative in all cases.

Case report – 1 (DVO)

A girl, first neurological symptoms occurred at 12 years, born from the second physiological pregnancy, psychomotor development was physiological without any abnormalities, menstrual cycle from 13 years, vaccinations in accordance with the Czech regulations and not associated with any complications; suffered from frequent tonsillitis; her mother committed suicide when the girl was 4 years old.

First neurological symptoms – central and left-sided, pyramidal and cerebellar hemisymptomatology, Expanded Disability Status Scale (EDSS)=3.5. MRI scans of the brain and cervical spine and the results of CSF examination and visual evoked potential (VEP) examination supported the diagnosis of MS. The girl was treated with pulse intravenous methylprednisolone (IVMP) at a dose of 3.0 g, achieving complete regression of the neurological symptoms (EDSS=1.0). Relapses 2 to 6 were experienced during the first 8 months of MS, usually straight after an infectious disease, always manifested as multifocal neurological symptomatology; MRI scans of disease activity repeatedly fulfilled the criteria of dissemination in space and time. IVMP pulse therapy at a dose of 3.0 g was administered 3 times in total. Continuous treatment with azathioprine 25 mg p.o. was initiated after relapse 4, i.e. 7 months after the first MS symptoms (M7). Relapse 5 (M8) with severe sensory-motor spinal symptomatology (EDSS=4.0) was treated with plasmapheresis (PE), 5 times every other day in total. Subjective and objective regression of the neurological deficit (EDSS=2.0) was observed from the third PE. An anxiety-depressive syndrome requiring symptomatic treatment persisted. At the same time, secondary hypogammaglobulinemia G was identified and was treated with repeated administration of intravenous immunoglobulines (IVIG) 15.0 g every 4 weeks. Relapse 6 (M9) was a relapse of sensory-motor symptomatology and was treated with a single IVIG pulse of 25.0 g and continued IVIG therapy with 15.0 g every 4 weeks, 9 doses in total. After 11 months of MS, DMD – GA therapy (COPAXONE 20.0 mg s.c. daily) was initiated, together with continued therapy with azathioprine 25.0 mg p.o. daily. Neurological deficit improved on this combined immunomodulatory and immunosuppresive therapy and mild regression of inactive demyelinating lesions was seen on MRI scans of the brain and cervical spine. The girl continued her attendance at an elementary school (year 8). After 11 months of remission, the girl experienced further relapses (7–11) with multifocal neurological symptomatology, with alternating paresis of the right and left lower limb, within MS M19 – M27. IVMP pulses were applied as a standard for every relapse, 3.0 g in total, with simultaneous combined treatment with GA and azathioprine 25.0 mg p.o. daily. Relapse 12 (M32) presented with alternating truncal as well as cerebellar symptomatology (EDSS=3.5) and with corresponding progression of the number of active cerebral and spinal white matter lesions shown in MRI scans (Figure **1** before therapy). The relapse was treated with IVMP pulses (3.0 g) followed by a total dose of 30.0 g of IVIG. This resulted in regression of neurological deficit (EDSS=1.5). After a total of 21 months of GA treatment, insufficient efficacy of the combined therapy prompted a "switch" (within the realm of DMD) to interferon-β (IFN-β) 22.0 ug s.c. 3 times weekly (M33). Continued combined therapy with IFN-β-1a with the same dose of azathioprine was complicated by further relapses (13 and 14) showing multifocal neurological, especially spinal, symptomatology with corresponding progression of the number and activity of lesions in cerebral and spinal MRI scans. Relapse 15 (M36) was associated with clinical deterioration of residual neurological symptomatology (EDSS=3.5) and thus was an

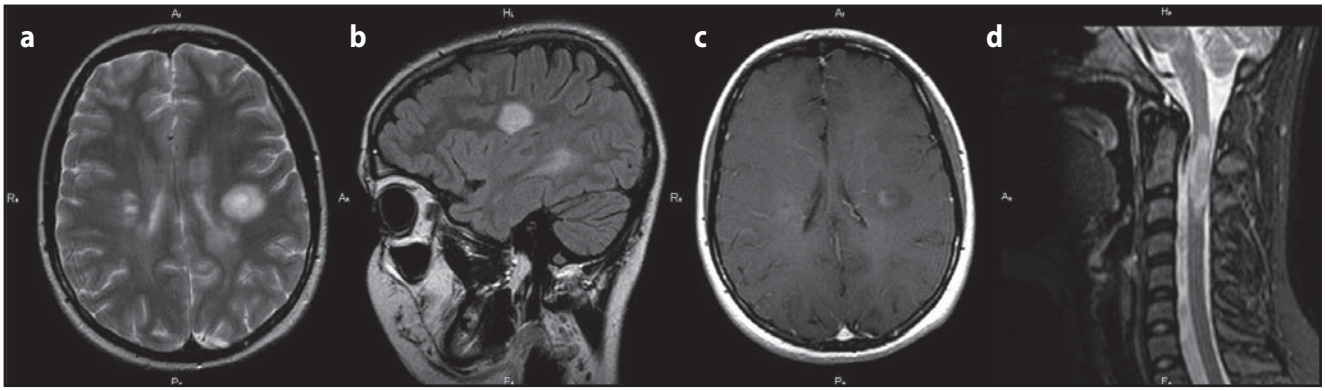

Fig. 1. Case study 1 – DVO1a–d before therapy. A voluminous, even tumor-like, lesion in the periventricular to juxtacortical frontal region on the left (a–c), with a marked "halo" in the periphery (a). Furthermore, multiple small lesions were repeatedly found in the periventricular region, some of the "dark hole" type on T1w scans (1c, 2c). Administration of contrast led to signal enhancement in the most voluminous lesion only; an incomplete ring-like saturation is relatively typical for a demyelinating disease. An enlarging voluminous lesion with a marked oedema in the periphery of the cervical spinal cord between the 1st – 2nd cervical vertebra in the STIR sequence (d).

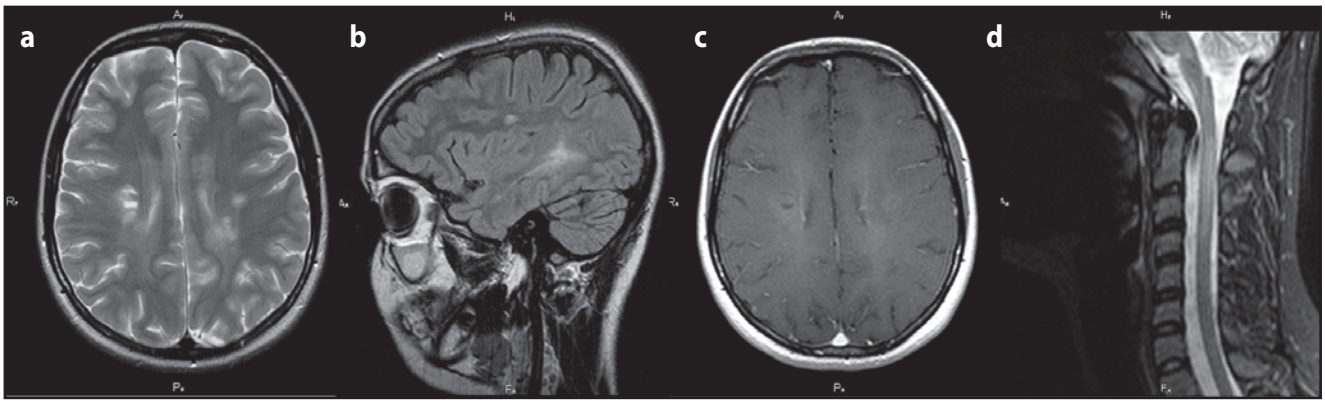

Fig. 2. Case study 1 – DVO2a–d after therapy. Clearly visible regression of the tumoriform lesion in the frontal region on the left, no peripheral "halo" (a, b); absence of opacification after contrast (c). Significantly reduced in size; oedema in the periphery of the intramedullar lesion regressed completely (d).

indication for escalation of therapy with natalizumab at a dose of 300.0 mg i.v., 36 months after the onset of the first MS symptoms (Figure 1). At the time of preparation of this report (Dec/2011), 30 natalizumab infusions were administered in total with no adverse effects, anti-JC virus antibodies were negative, the patient had minimal neurological deficit (EDSS=1.5) and presented with no relapse from the initiation of natalizumab therapy and with regression of lesions on cerebral and spinal MRI scans (Figure 2). Currently, the girl is a student at a school of floral design, year 3.

Case report – 2 (BUR)

A girl, the first neurological symptoms occurred at 15 years; born from the second physiological pregnancy, psychomotor development physiological, menstrual cycle from 14 years, vaccination in accordance with the Czech regulations and without complications. Her brother has Crohn's disease and grandmother has polyomyositis. During her preschool age, the girl experienced repeated herpetic infections treated with acyclovir. Iridocyclitis in the left eye at 11 years. The first neurological symptomatology occurred at 15 years; sensory, pyramidal and cerebellar symptomatology was more pronounced on the left-sided limbs, while visual nerve inflammation on the right (EDSS=3.5). MRI showed characteristic cerebral and spinal demyelinating lesions (Figure 3), CSF investigation identified 14 oligoclonal bands, microscopic examination confirmed 22/3 lymphocytes, and there was an abnormal response in somatosensory evoked potentials (SSEP). IVMP pulse treatment at a total dose of 3.875 g (6-day IVMP therapy protocol: 3×1000 mg; 1×500 mg; 1×250 mg; 1×125 mg) was indicated with subsequent tapering dose of methylprednisolone (MP) p.o. (MP p.o. dose reduced every 3 days: 48 mg; 32 mg; 16 mg; 8 mg) with a minimum residual sensory deficit of the spinal type (EDSS=1.0). Follow up cerebral and spinal MRI scan obtained 3 months later (M3) showed progression of activity and the number of the lesions. Subclinical relapse was treated with IVMP pulses (3.875 g) that led to dermal adverse effects (erythema, acne and striae).

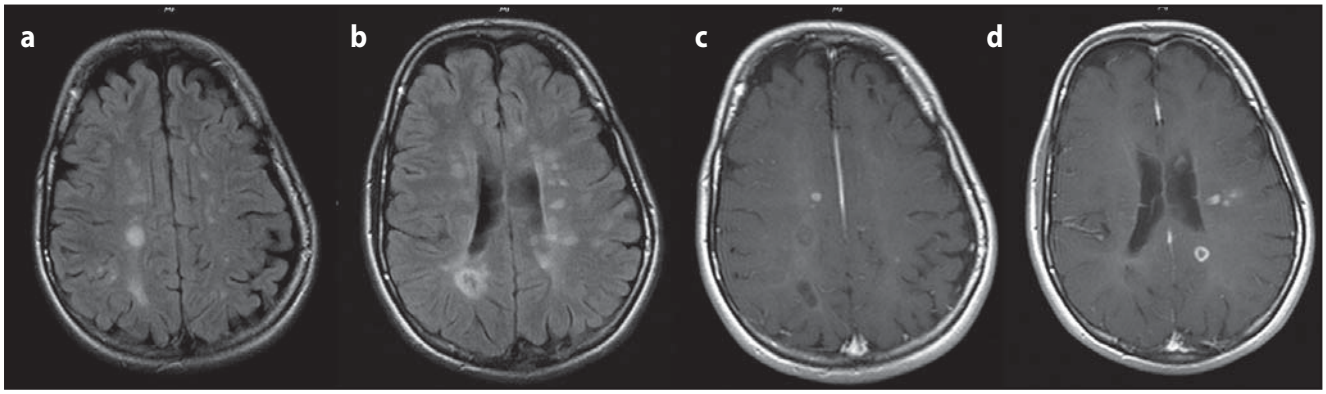

Fig. 3. Case study 2 – BUR1a–d before therapy. Multiple small lesions in the peri- and paraventricular region in supratentorial white matter (a, b); voluminous pseudocystic lesion above the trigone of the lateral ventricle on the right – equivalent to "black hole". Contrast-enhanced lesions on T1w images using the magnetization transfer (MT) technique (c, d). Lesions enhanced annularly as well as in the entire volume confirm high activity of the disease.

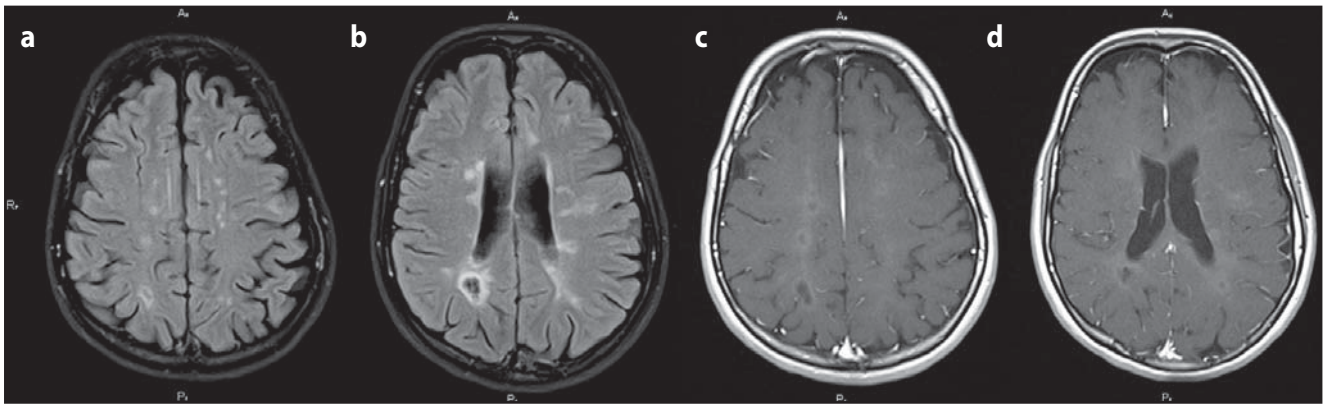

Fig. 4. Case study 2 – BUR2a–d after therapy. Clearly visible retraction of the lesions and reduction in their size on FLAIR scans (a–b); marked regression of the lesion found in the frontodorsal region on the right. Better delineation of the pseudocystic lesion above the trigone on the right. No significant increase in T1 signal corresponding to impaired hematoencephalic barrier was observed after administration of contrast (c, d). Discrete annular enhancement of the signal in the periphery of the lesions is not caused by saturation with the contrast but by impaired white matter structure. Signal obtained using MT technique is not reduced at such locations.

Subsequently, DMD therapy was initiated (M4) – IFN-β-1a 30 μg i.m. once weekly in combination with IVIG 15.0 g every 4 weeks. Dual immunomodulatory therapy was administered for 3 months and was regularly complicated with the flu-like syndrome upon application of IFN-β-1a i.m. that required symptomatic treatment. Relapse 3 (M8) had truncal symptomatology, sensory and pyramidal in the limbs and sensory-motor in cerebral nerves CN V and VII (EDSS=3.5). Cerebral MRI scan showed dramatic progression of the number of active demyelinating lesions particularly in the supratentorial region (Figure 3). IVMP pulse therapy (3.875 g) was initiated and MP subsequently tapered-out. A standard wash-out period was allowed before initiating therapy with natalizumab 300.0 mg i.v. every 4 weeks. During the wash-out period, the girl experienced relapse 4 (M9) with mild, left-sided, sensory, pyramidal and cerebellar hemisymptomatology. Natalizumab therapy escalation was initiated 10 months after the first manifestation of neurological symptomatology due to high level of MS activity and insufficient efficacy of dual immunomodulatory treatment (stopped after 4 months). Six infusions of natalizumab supplemented with therapeutic rehabilitation led to regression of neurological deficit (EDSS=2.5). Follow up brain MRI performed 12 months post natalizumab therapy initiation (Figure **4**) showed regression in terms of size and activity of lesions. At the time of preparation of this report (Dec/2011), a total of 20 infusions of natalizumab were administered with no adverse effects, anti-JC virus antibodies were negative and there was residual neurological deficit (EDSS=2.0). From the initiation of natalizumab therapy, the patient had no relapse and cerebral MRI showed regression of lesions (Figure **4**). The girl has now enrolled in the first year of a college of law and public service.

Case report – 3 (BAZ)

A boy, first neurological symptomatology occurred at 16 years, born from the first physiological pregnancy, psychomotor development was physiological, vaccination in accordance with Czech regulations and without

complications. His grandparents were smokers and the boy came into contact with smoking environment from early childhood. The first manifestation of alternating neurological symptomatology, pyramidal in the limbs and motor in cerebral nerves (CN VII) on the right (EDSS=2.5), was recorded at 16 years. Cerebral MRI revealed multiple demyelinating lesions at characteristic locations, with activity visible in the supra- and infratentorial regions (Figure 5). CSF investigation showed 2 oligo IgG bands, microscopic examination showed 46/3 lymphocytes and VEP identified P100 wave abnormality on the right. The boy was treated with IVMP pulses (3.0 g) with subsequent tapering dose of MP. The therapy was complicated by arterial hypertension. After 7 months, relapse 2 occurred with prolonged truncal neurological, pyramidal and sensory symptomatology (EDSS=3.0) and corresponding progression of the activity and number of demyelinating lesions shown on cerebral MRI scans. Considering the significant intolerance of steroid therapy, a series of PE every other day was initiated. This therapy resulted in decline in fibrinogen values to 0.77 g/l (normal range: 1.0–3.8 g/l) and was, therefore, discontinued. In spite of that, 3 completed PEs led to a significant regression of neurological deficit with a minimal residual disability score (EDSS=1.5). Relapse 3 with pyramidal neurological symptomatology (EDSS=2.0) occurred just over a month later (M9); the boy was treated with IVMP pulses (3.0 g) with subsequent tapering dose of MP p.o. Steroid therapy was associated with acne and depression (no arterial hypertension this time), treated symptomatically with antidepressants and psychotherapy. Clinically definitive highly active MS with 3 relapses in 9 months and progressive development of demyelinating lesions on MRI (Figure 5) were an indication for natalizumab 300.0 mg i.v. every 4 weeks treatment initiation, 10 months after the first symptoms of MS. No adverse reactions and no relapses were observed. Follow up cerebral MRI scans (Figure 6) showed reduced volume and activity of contrast-enhanced lesions. At the time of preparation of this report (Dec/2011), a total of 19 infusions of natalizumab were administered with no adverse effects, anti-JC virus antibodies were negative and the patient had minimal residual neurological deficit (EDSS=1.5). Currently, the boy is studying at a university, year 3.

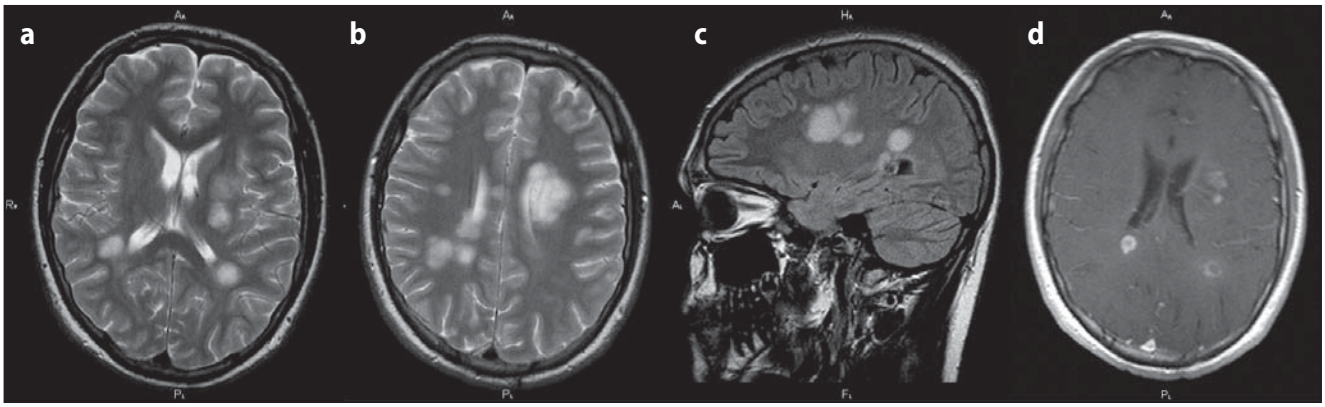

Fig. 5. Case study 3 – BAZ1a–d before therapy. Marked focal involvement of supratentorial periventricular white matter, slightly expanding T2 and FLAIR (a–c) hyperintense lesions in the frontal and parietal regions. Impairment of hematoencephalic barrier shown on T1 weighted (T1w) scans using the MT technique in order to obtain higher contrast of the contrast-enhancing lesions. Typical annular nature of the lesions; post-contrast saturating areas (d) have their equivalent in "halo" on T2w scans (a, b).

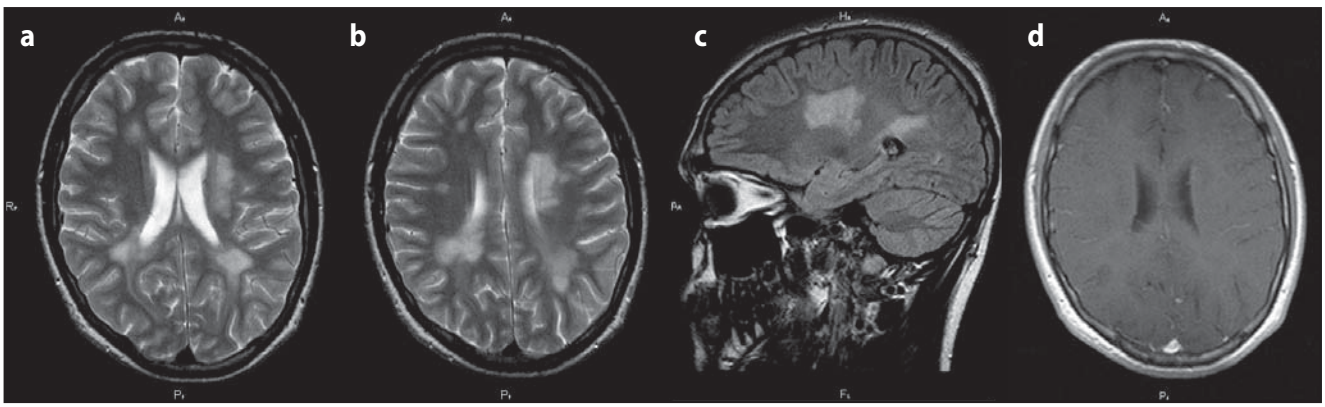

Fig. 6. Case study 3 – BAZ2a–d after therapy. Reduced volume of the lesions on T2w and FLAIR (a–c), the lesions do not exhibit any apparent peripheral "halo" (a, b). No evidence of hematoencephalic barrier impairment was found after contrast application in the areas with demonstrated high activity of the disease before therapy (d).

Case report – 4 (HAN)

A girl, the first neurological symptomatology occurred at 13 years, born from the second uncomplicated pregnancy, psychomotor development physiological, appendectomy at 6 years, menstrual cycle from 12 years of age. In addition to vaccination in accordance with the Czech regulations, the girl was vaccinated against varicella (VARILRIX). Acute central vestibular and cerebellar symptomatology (EDSS=2.5) was observed 4 days post hepatitis B vaccination (ENGERIX). Cerebral and spinal MRI scans showed (Figure 7) multifocal hyperintense lesions of characteristic locations in the periventricular and infratentorial regions and with no involvement of cervical spine. Evidence of 10 oligoclonal IgG bands was found in the cerebrospinal fluid, cells – 9/3 lymphocytes, VEP abnormality with bilateral prolongation of P100 wave latency. The girl was treated with IVMP pulses at a total dose of 3.875 g (6-day therapy protocol: 3x1000 mg; 500 mg; 250 mg; 125 mg) with subsequent tapering dose of MP p.o. (MP dose was reduced every 3 days: 48 mg; 32 mg; 16 mg; 8 mg) with gradual regression of neurological symptomatology (EDSS=1.5). Steroid therapy was complicated by amenorrhea. Relapse 2 occurred 10 months later in connection with physical strain (ski course in the mountains, 1 week) and was associated with truncal syndrome with diplopia and central vestibular and cerebellar symptomatology (EDSS=2.5). Cerebral MRI scans showed a new active lesion, juxtacortical distribution of the lesions and stationary image of periventricular lesions. The girl was treated with IVMP pulses (3.875 g) with subsequent tapering dose of MP p.o.; at the same time, immunosuppression was initiated with azathioprine at a dose of 25 mg p.o. daily, reduced to 25 mg p.o. every other day after 3 months. This treatment regime was followed by gradual regression of the acute relapse (EDSS=1.5). Follow up cerebral MRI scan after 6 months showed progression in terms of the number of active hyperintense lesions. Subclinical relapse 3 (M16) was treated with a standard IVMP protocol (3.0 g) with subsequent tapering dose of MP p.o. After 3 relapses, 24 months from manifestation of the first MS symptoms, DMD – GA therapy was initiated at a dose of 20 μg s.c. daily. A follow up cerebral MRI performed 12 months after the initiation of combined therapy with GA 20.0 ug s.c. daily and azathioprine 25.0

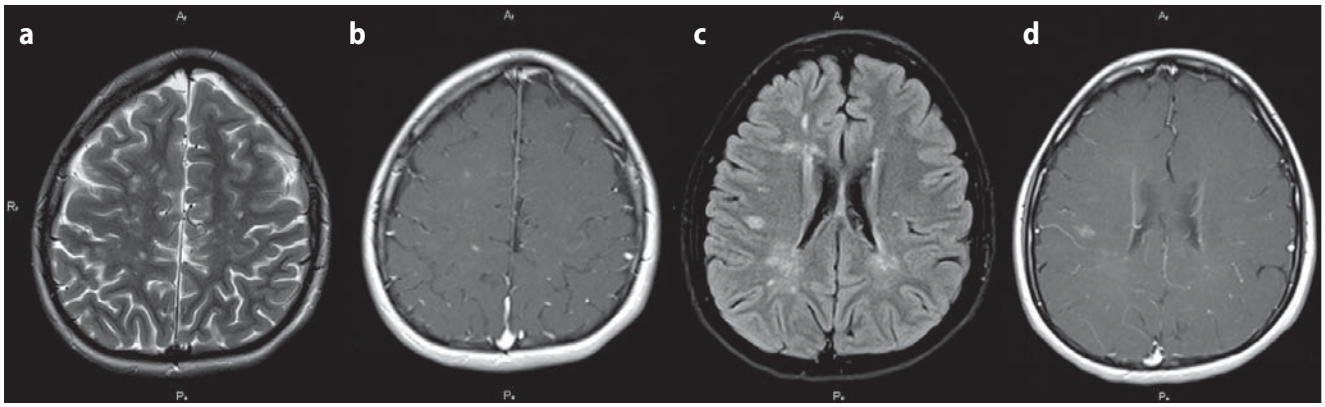

Fig. 7. Case study 4 – HAN1a–d before therapy. In this patient, disease activity is demonstrated in a form of rather small lesions (a, c); in the supratentorial region, virtually in all layers of white matter, well visible on T2w and FLAIR. Compared to previous visits, a new lesion with blurred edges is visible in paraventricular white matter, in the frontal region on the right (c) with marked enhancement of T1 signal after contrast application using MT technique (d). Two additional small active lesions immediately below the convexity also enhanced their signals after intravenous administration of paramagnetic contrast agent (b).

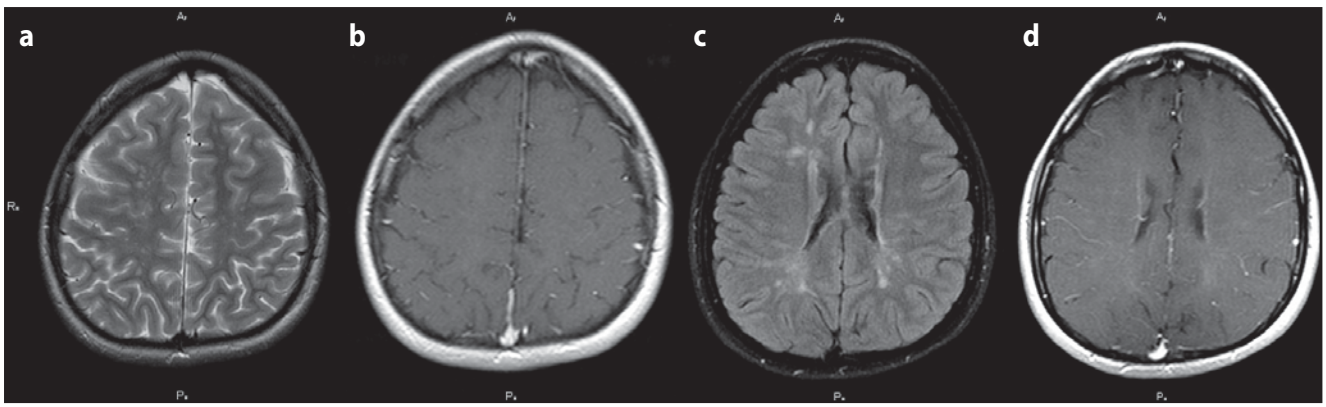

Fig. 8. Case study 4 – HAN2a–d after therapy. Almost complete regression of the originally active, voluminous lesion in the frontal region on the right (c); no lesion increased its signal after an administration of contrast (b, d). The size of other lesions was also slightly reduced (a, c).

mg p.o. every other day showed additional new, active hyperintense contrast-enhanced lesions. Subclinical relapse 4 (M36) was treated with the standard IVMP protocol (3.0 g) with subsequent tapering dose of MP p.o. Steroid therapy was associated with menstrual cycle disorder; clinical disability score was assessed as EDSS=1.5; the girl was studying at the first year of a college of economics. A follow up cerebral contrast-enhanced MRI scan after 24 months of combined immunomodulatory and immunosuppressive therapy showed progression of subclinical activity again, indicating new active lesions in the supra- and infratentorial regions. Subclinical relapse 5 (M47) was treated with standard IVMP steroids (3.0 g) and MP p.o. The first-line MS therapy with DMD (GA) in combination with immunosuppression was assessed as providing insufficient efficacy. Wash-out period of 6 months was applied after azathioprine discontinuation with the aim to escalate the MS therapy with natalizumab. Follow up MRI further 3 months later showed new active lesions again. This subclinical relapse 6 (M50) was treated with standard steroid regimen (IVMP (3.0 g) and MP p.o.). Treatment escalation with natalizumab 300.0 mg i.v. every 4 weeks was initiated 53 months after the first MS symptoms. Of these 53 months, combined first-line therapy (DMD-GA, azathioprine) was administered for 24 months but provided insufficient efficacy. Anti-JC virus antibodies were negative, natalizumab therapy was tolerated very well. There was no clinical relapse and follow up cerebral MRI scan after 6 months of therapy (Figure 8) showed complete regression of active lesions and regression of existing lesions with no increase of their number. At the time of preparation of this report (Dec/2011), 6 natalizumab infusions were administered in total with no adverse effects, EDSS=1.5; the girl is currently studying at a college, year 2.

Case report – 5 (FID)

A boy, the first neurological symptoms occurred at 9 years, born from the first physiological pregnancy, psychomotor development normal; experienced febrile spasms in the first year of life, varicella at 6 years; both parents are on therapy due to primary epilepsy; in addition, the mother suffers from sarcoidosis and

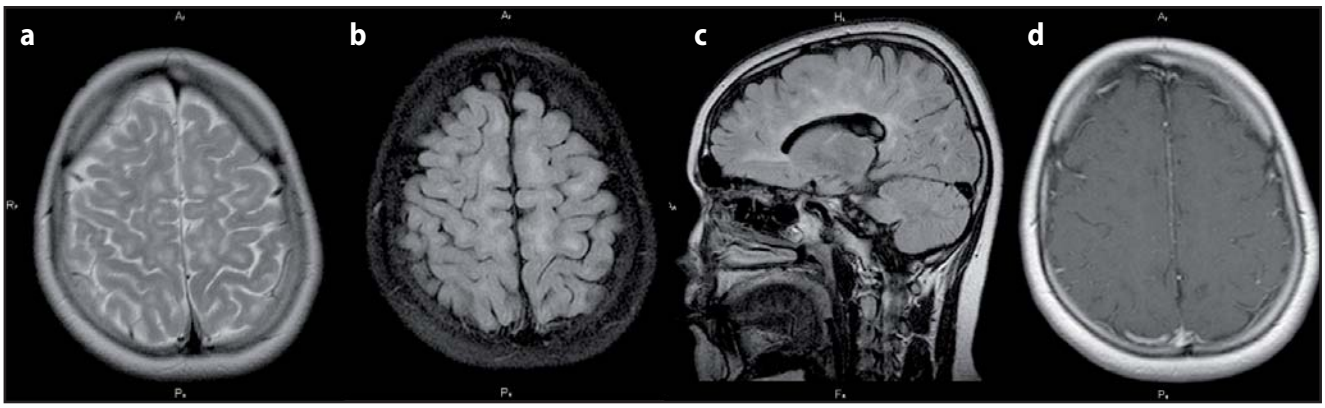

Fig. 9. Case study 5 – FID1a–d before therapy. Massive coalescing focal involvement of the white matter in the supratentorial, predilection juxtacortical and subependymal regions, with a typical development of lesions (a–c). A new hyperintense lesion visible on T2 and FLAIR in the frontodorsal, precentral region on the right, high below the convexity. The lesion clearly enhanced its signal after contrast application on T1w MT. Again, the lesion showed an annular nature of saturation.

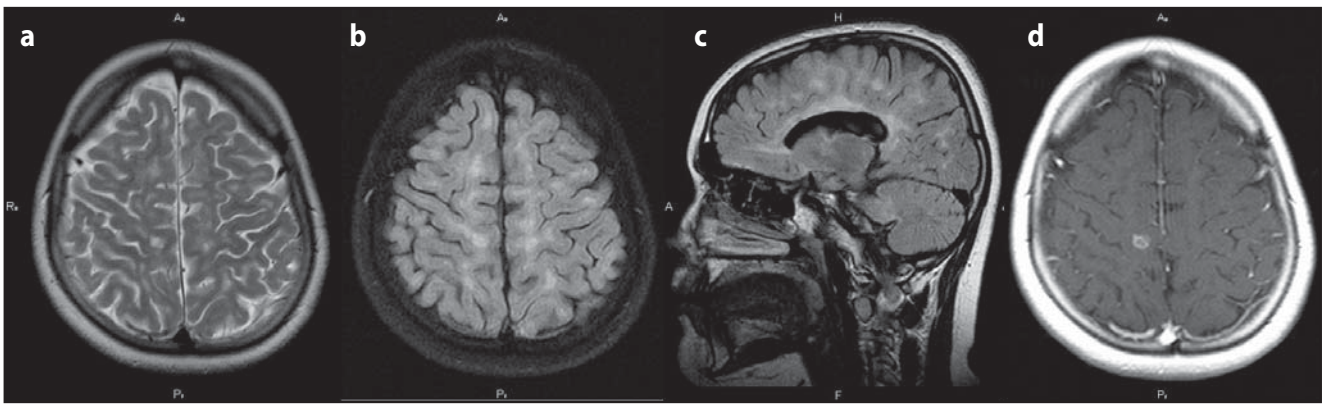

Fig. 10. Case study 5 – FID2a–d after therapy. Stationary number and volume of lesions (a–c); reduced volume of a previously active lesion (a, b), the lesion is difficult to differentiate from the surrounding lesions. No signal enhancement in the lesion or in the surrounding tissue after contrast application (d).

one grandmother from MS. Sudden development of vestibular, cerebellar and quadrupyramidal symptoms occurred at 9 years. Cerebral and spinal MRI scan showed massive involvement of white matter with blending lesions in the supratentorial, predilection juxtacortical and subependymal regions (Figure 9); microscopic examination showed 20/3 lymphocytes and CSF contained 5 oligoclonal IgG bands; bilaterally extended latency of P100 wave on VEP. Extensive clinical finding (EDSS=2.5) and cerebral MRI results, CSF and VEP supported the diagnosis of the first MS attack, thus the boy was indicated for IVMP pulse therapy (5.0 g) with tapering dose of MP p.o., complicated by arterial hypertension and secondary cushingoid obesity. Due to limited efficacy and poor tolerance of steroid therapy, a single IVIG 2.0 g/kg was administered for 2 days at another department. After 8 months, relapse 2 occurred with neurological alternating truncal symptomatology, quadrupyramidal and involving CN VII (EDSS=2.5) with progression of the number and activity of focal involvement of white matter on cerebral MRI. The boy was treated with IVMP pulses (3.0 g) with subsequent tapering dose of MP p.o., resulting in mild regression of neurological symptoms (EDSS=2.0). Follow up cerebral MRI after 27 months showed activity and progression of extensive white matter involvement. Subclinical relapse 3 (M36) was treated with IVMP pulses (3.0 g). Neurological disability score EDSS=2.0. Follow up cerebral MRI after further 3 months showed activity progression again, as well as involvement of white matter of the brain and multiple lesions in the cervical and thoracic spinal cord. Subclinical relapse 4 (M39), disability score EDSS=2.5. Natalizumab 300.0 mg i.v. every 4 weeks was selected as primary therapy to manage this rapidly developing disease with massive involvement of cerebral and spinal white matter. No signs of relapse were present 6 months of very well tolerated therapy, anti-JC virus antibodies were negative, neurological deficit stationary, EDSS=2.0. Follow up cerebral MRI (Figure 10) showed stable volume of white matter lesions, with no signal enhancement after contrast application. At the time of preparation of this report (Dec/2011), the boy was 13 years old, has undergone 6 natalizumab infusions without any adverse effects, he had no relapse, and studied at a primary school, year 7.

DISCUSSION

MS therapy should, irrespective of patient age, fulfil two essential requirements. First, it should activate or substitute immunosuppresive mechanisms affecting immune reactivity during a relapse and/or affecting any other form of disease activity (e.g. Gd enhancing lesions on MRI). Second, it should eliminate pathophysiological processes that affect disease progression and related symptoms during a remission using disease modifying drugs (DMD) and symptomatic therapy.

The presented case reports contribute to evidence base on the use of natalizumab in children where the first-line DMD therapy lacked efficacy, including its use in combination with steroid pulse therapy, plasmapheresis and, in one case, with intravenous immunoglobulins or azathioprine immunosuppresion. In two children, boys (BAZ-3; FID-5), natalizumab was the treatment of first choice initiated 10 months (BAZ-3) and 39 months (FID-5), respectively, after the onset of MS symptoms and was selected to manage high disease activity and poor efficacy of steroid pulses, together with their reduced tolerance and adverse effects. The use of natalizumab in children with high MS activity and poor tolerance of the first-line therapy was in accordance with the available literature (Borriello et al 2009; Huppke *et al.* 2008). These cases confirm that MS therapy must not only be timely, initiated preferably after the first MS attack but that the most effective modality for the given patient should be selected, even if such treatment does not comply with age-related prescribing restrictions, as in these two cases. This approach fulfils requirements for individualized therapy, i.e. early treatment initiation with the most efficacious modality possible for the patient's specific phase and form of MS. Natalizumab posology in children has not been determined yet. Two approaches, identical to adult patients, can be found in literature, i.e. 3.0–5.0 mg/kg/dose or 300.0 mg/dose. Dosing as low as 3.0 mg/kg/dose was identified as efficient, as described in a clinical study of Crohn's disease where the alpha-4 integrin receptor was saturated to 93% 2 hours after the first infusion and to 40% after the third infusion with this low dose (Hyams *et al.* 2007). The children presented here had varied duration of natalizumab therapy (30, 20, 19, 6 and 6 months); however, they showed identical regression of their MRI lesions as soon as 6 months into their therapy, (Figures 2,4,6,8 and 10), regression of the clinical syndrome with no further relapses, and neurostatus stabilization. This corresponds to the reported rapid onset of effect of natalizumab therapy leading to a reduction in the number of Gd enhancing lesions and T2 hyperintense lesions in the majority of (58–95%) patients (Borriello *et al.* 2009).

The available literature mostly suggests using the same natalizumab dosing regimens in children with MS as in adults (Ann Yeh & Weinstock-Guttman 2010). The dosing regimen of 300.0 mg/dose natalizumab was also used in the five children presented in this paper. The efficacy of this therapy may be affected by development of antibodies against natalizumab. Transient anti-natalizumab antibodies were found, in 3% and permanent in 6% of SENTINEL and AFFIRM study patients (Calabresi *et al.* 2007). Compared to patients with negative titer, permanently positive titer of anti-natalizumab antibodies was associated with increased disability progression, relapse rate and number of MRI lesions (Calabresi *et al.* 2007; Polman *et al.* 2006).

In the above mentioned clinical studies in adult patients, hypersensivity reactions, allergic reactions or anaphylactoid reactions occurred in 4% of patients only (Polman *et al.* 2006). One pediatric case has been described in literature where therapy had to be discontinued due to a hypersensitivity reaction associated with a development of anti-natalizumab antibodies (Ann Yeh & Weinstock-Guttman 2010).

Currently, progressive multifocal leukoencephalopathy (PML) is the most serious and the most feared complication of natalizumab therapy. Long-term natalizumab therapy leads to lasting improvement in the neurological condition but also compromises immune surveillance. In some individuals, this may lead to a development of a serious opportune infection with the John Cunningham virus (JCV). The overall incidence of PML in clinical trials with natalizumab in more than 3000 MS patients has been estimated at 1 per 1000 (Sørensen *et al.* 2012). PML is diagnosed with MRI where large or even coalescing non-Gd enhancing lesions, are found. The presence of JCV DNA in CSF determined by RT-PCR (polymerase chain reaction with reverse transcription) is a clear proof. No therapy is known. Even though there frequently is a significant neurological deficit, survival of up to 80% of patients is achieved with immediate discontinuation of natalizumab and its rapid elimination from the body using plasmapheresis. The resulting disability depends on an early diagnosis and IVMP administration to manage the Immune Reconstitution Inflammatory Syndrome (IRIS). IRIS is a manifestation of the immune system restoration process and occurs within approximately 4 weeks after termination of natalizumab therapy. MRI correlate consists of enlarging, Gd-enhancing lesions (Yousry *et al.* 2006). No PML case related to natalizumab therapy have been described in children with MS treated with natalizumab. However, the number of treated children does not exceed several dozen worldwide (Banwell *et al.* 2006; Borriello *et al.* 2009; Huppke *et al.* 2008; Yeh & Weinstock-Guttman 2010). In pediatric population, several cases of PML have been linked to the primary immunodeficiency syndrome such as the Wiskott-Aldrich syndrome (Katz *et al.* 1994). JCV presence in the urine and/or serum is not an early PML marker but helps to stratify the risk for patients on natalizumab therapy. Studies indicated that less than 25% of immunocompetent children were infected with JCV, whereas their number rises with age; less than 15% of children younger than 10 years were infected with JCV. The risk of reactivation of asymptomatic JC virus infection in children appears to be very low. At present, the contribution made by previous immunosuppresive therapy to the overall risk of PML in natalizumab-treated patients needs to be established; previous immunosuppresive therapy is generally considered to be a significant risk factor of PML that is, however, difficult to quantify. PML risk raises in adult patients with previous immunosuppresive therapy from 0.66/1000 of treated patients during the first 24 months of treatment with natalizumab to 4.3/1000 during 24–48 months of therapy (13). There was a total of 95,300 treated patients in December 2011, with 193 registered PML cases, of whom 39 (20%) died.

Malignancy represents another serious complication of natalizumab therapy, although its prevalence does not exceed 1%. No malignancies have been observed in children with MS treated with natalizumab. The prevalence of primary CNS lymphoma in children is 0.02/100,000 and it is expected that previous immunosuppression may be a predisposing factor for an increased risk of primary CNS lymphoma. Therefore, highly cautious approach should be exercised in children on natalizumab therapy in respect to these issues (Yeh & Weinstock-Guttman 2010).

CONCLUSION

Natalizumab is a promising and clearly efficient treatment modality for children with MS who present with an aggressively developing disease and insufficient response to first-line therapy. Monitoring of anti-JCV antibodies is advisable to identify PML risk in children with MS on natalizumab therapy. The question on how and when to decide to terminate treatment with natalizumab in children with MS remains to be answered.

Declaration of conflicting interests

Dr. R. Talab reports having received lecture fees from Biogen Idec, Merk/SERONO, NOVARTIS, Sanofi-Aventis, TEVA, Bayer/Schering. Dr. M. Talabova reports having received lecture fees from TEVA, SERONO, Sanofi-Aventis. Dr. L. Klzo has nothing to declare.

REFERENCE

1 Ann Yeh E and Weinstock-Guttman B (2010). Natalizumab in Pediatric Multiple Sclerosis Patients. Ther Adv Neurol Disorders. **3**(5): 293–299.

2 Banwell B, Reder AT, Krupp L, et al. (2006). Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis. Neurology. **66**: 472–476.

3 Bauer HJ, Hanefeld FA (1989). Multiple Sklerose in Kindesalter. In: Hanefeld FA, Rating D, Christen HJ, eds. Aktuelle Neuropediatrie. Berlin: Springer-Verlag, 285–298.

4 Borriello G, Prosperini L, Luchetti A and Pozzilli C (2009). Natalizumab treatment in pediatric multiple sclerosis: a case report. Eur J Paediatr Neurol. **13**: 67–71.

5 Calabresi PA, Giovannoni G, Confavreux C, et al. (2007). The incidence and significance of antinatalizumab antibodies: results from AFFIRM and SENTINEL. Neurology. **69**: 1391–1403.

6 Ghezzi A, Amato MP, Annovazzi P, et al. (2009). Long-term results of immunomodulatory treatment in children and adolescents with multiple sclerosis: the Italian experience. Neurol Sci. **30**: 193–199.

7 Hanefeld FA, Christen HJ, Kruse B, Bauer HJ (1993). Childhood and juvenille multiple sclerosis. In: Bauer HJ, Hanefeld F. Multiple sclerosis. It´s Impact from Childhood to Old Age. London: WB Saunders: 14–52.

8 Havrdova E (2007). Léčba roztroušené sklerózy. Remedia.**17**: 61–72.

9 Havrdova E (2010). Současné možnosti léčby roztroušené sklerózy. Remedia. **20**: 278–282.
10 Huppke P, Stark W, Zurcher C, Huppke B, Bruck W and Gartner J (2008). Natalizumab use in pediatric multiple sclerosis. Arch Neurol. **65**: 1655–1658.
11 Hyams JS, Wilson DC, Thomas A (2007). The International Natalizumab CD305 Trial Group Natalizumab therapy for moderate to severe Crohn disease in adolescents. J Pediatr Gastroenterol Nutr. **44**(2): 185–91.
12 Kappos L, Bates D, Edan G, et al. (2011). Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurology. **10**: 745–758.
13 Katz DA, Berger JR, Hamilton B, Major EO and Post MJ (1994). Progressive multifocal leukoencephalopathy complicating Wiskott-Aldrich syndrome. Report of a case and review of the literature of progressive multifocal leukoencephalopathy with other inherited immunodeficiency states. Arch Neurol. **51**: 422–426.
14 Masterman T, Ligers A, Olsson T, et al. (2000). HLA-DR15 is associated with lower age at onset in multiple sclerosis. Ann. Neurol. **48**: 211–219.
15 Mikaeloff Y, Caridade G, Assi S, et al. (2007). Hepatitis B vaccine and risk of relapse after a first childhood episode of CNS inflammatory demyelination. Brain. **130**: 1105–1110.
16 Mikaeloff Y, Caridade G, Tardieu M, and Suissa S (2008). Effectiveness of early beta interferon on the first attack after confirmed multiple sclerosis: a comparative cohort study. Eur J Paediatr Neurol. **12**: 205–209.
17 Mikaeloff Y, Caridade G, Tardieu M, Suissa S (2007). Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. Brain. **130**: 2589–2595.
18 Mikaeloff Y, Caridade G, Tardieu M, Suissa S (2009). Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. Neurology. **72**: 873–880.
19 Neumann H (2003). Molecular mechanisms of axonal damage in inflammatory central nervous system diseases. Curr Opin Neurol. **16**: 267–273.
20 Polman CH, O´Connor PW, Havrdova E, et al. (2006). A randomised, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. **354**: 899–910.
21 Sørensen PS, Bertolotto A, Edan G et al. (2012). Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. Mult. Scler. J. **18**(2): 143–152.
22 Yousry TA, Major EO, Ryschkewitsch C, et al. (2006). Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. **354**: 924–933.