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Clinico-immunogenetic characteristics of multiple sclerosis with optic neuritis in children

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The frequency of multiple sclerosis (MS) with clinical onset before 16 years of age in different regions of Russia fluctuates from 2 to 10% of all MS patients. One of the most frequent signs of MS manifestation and/or exacerbation at this age is optic neuritis (ON). Forty-seven children with MS were observed in Moscow. Diagnosis of MS in every case was clinically definite and proved by serial MRI. Clinico-tomographic dissociation was noticed: numerous large lesions, typical for MS on T2 images were often seen in children with mild or moderate residual neurological symptoms. All patients had relapsing/remitting MS course, mean EDSS was 2.24 ± 0.26. Thirty-eight children (80%) had ON at least once, ten (21.3%) – twice or more times. In several cases ON had subclinical course or might be missed and the damage of the optic nerve with partial atrophy was found only after complex ophthalmological investigation including visual evoked potentials. Thus, the clinical course of MS and ON have some peculiarities in children and may be genetically based. Analyses of allelic polymorphisms of HLA-DR and TNF loci on chromosome 6 was performed. Data from children with MS were compared with data from their parents, healthy controls and other MS patients from the same ethnic group. Children with MS had increased frequency of DR2(15) and TNF-a11, but not TNF-a9 as adult MS patients from the same ethnic group. The presence of TNF-a7, rare in adult patients, could be proposed as a marker of early MS onset. *Journal of NeuroVirology* (2000) **6,** S152 – S155.

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Introduction

Russia is in the zone of medium MS frequency, the ratio of MS prevalence fluctuates from 15 to 70 per 100 000 of population (Boiko 1994; Boiko *et al*, 1995). Cases with early MS onset are registered in different regions of Russia, the frequency of MS with clinical manifestation before age 16 fluctuates in Russia from 2 to 10% of all MS patients (Guseva, 1994), which is in concordance with other countries (Duquette *et al*, 1987).

Childhood MS requires more and more attention and specific management (Hanefeld, 1998). The most frequent MS in children starting from age 10 to 13 years, while more early MS manifestations were also described (Izquierdo *et al*, 1986; Hauser *et al*, 1982; Baidina and Shutov, 1990; Hanefeld *et al*, 1991; van Lieshout *et al*, 1993). The disease was reported to have some clinical peculiarities at this age: predominance of girls, brainstem symptoms and optic neuritis are characteristic (Hauser *et al*, 1982; Hanefeld *et al*, 1991; Guseva, 1994; Guilhoto, 1995; Hanefeld, 1998). As a rule childhood MS has relapsing/remitting course, rarely secondary progressive (Duquette *et al*, 1987; Baidina and Shutov, 1990).

Genetic studies of childhood MS are very rare. Serological investigations showed possible peculiarities in HLA class I locus (Efrimenko *et al*, 1995). Recently high frequencies of secondary Lebus hereditary optic neuropathy (LHON) mutations np 4213, 4917 and 13708 of mitochondrial DNA was reported in children with MS and ON (Ohlenbusch *et al*, 1997; Hanefeld, 1998), while the significance of these genetic peculiarities is not high and should be

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studied further (Ohlenbusch *et al*, 1998; Wilichowski *et al*, 1998). The aim of our study was to investigate clinico-immunogenetic peculiarities of children with MS and ON from the Russian ethnic group.

Results

Forty-seven children with definite MS according to Poser criteria were included in the study. Main clinical characteristics of these patients are in Table 1. All patients have relapsing/remitting not severe MS course, only six patients (12.8%), secondary progressive. Mean age of MS onset was 11.46, in the majority of children MS started from 10 to 14 years of age, the earliest onset of MS in our group was a girl with optic neuritis appearing at 4 years of age. Mean EDSS ratio 2.24 ± 0.26. The most frequent residual clinical symptoms were signs of optic nerve involvement, pyramid signs and eye movements disorders. There was no statistically definite association between vaccination or any specific childhood infection and the manifestation of MS, while 73.3% had chronic tonsilitis with or without tonsillectomy.

Thirty-eight children with MS (80%) had ON at least once, while ten of them (21.3%) twice or more.

Table 1 Main clinical characteristics of 47 children with MS clinical onset at age before 16 years

Characteristics	*Children with MS*
Gender	26 girls and 21 boys
Mean age of onset	11.46 ± 0.41
Mean EDSS ratio	2.24 ± 0.26
Relapsing/remitting course	47 (100%)
secondary progressive	6 (12.8%)
Mean number of relapses	3.04 ± 0.22
Decrease of vision acuity/fields	38 (80.9%)
Pyramid signs	36 (76.6%)
Eye movement disorders	21 (44.7%)
Sensory disturbances	20 (42.6%)
Cerebellar signs	15 (31.9%)

In 18 cases (38%) ON was a MS clinical manifestation. Often signs of sub-clinical optic neuritis were found only after complex ophthalmologic observation (perimetry, contrastometry, visual evoked potentials). In comparison to adult MS patients children with MS and optic neuritis had less frequent headaches, occular pain, two-side involvement and progressive course of optic neuritis, but more often severe oedema and papillitis, seen at the ophthalmoscopy. There was a disassociation between the degree of the loss of visual function and the ophthalmoscopic picture that was seen. Decrease in visual acuity and changes in visual fields could be accompanied with the normal ophthalmoscopic picture and the features of partial optic nerve atrophy might appear in the period of restoration of vision. Dystrophic changes were observed at ophthalmoscopy in 28 patients (59.6%) from this group.

The multiple damage of white matter was in every case proved by serial MRI. Typical lesions of high intensity were seen on T2 scans. The majority of children had from four to ten lesions. Large periventricular lesions with a diameter higher than 2 sm were frequent, while on the whole characteristics of lesions were the same as in adult MS patients. This has been noted also in other studies (Golden and Woody, 1987). A clinico-tomographic dissociation could be proposed for childhood MS: mild or moderate disease course often could be accompanied by numerous large lesions on T2 MRI scan.

Previous genetic studies showed, that MS patients from this ethnic group had increased frequencies of DR2(15), TNF-a1 TNF-a9 and decreased TNF-a7 (Gusev *et al*, 1997a; Sudomoina *et al*, 1998). Increase of TNF-a1 frequency was also seen in the Norwegian ethnic group (Gusev *et al*, 1997b), while in other Caucasians increase of TNF-a11 frequency was found (Roth *et al*, 1994). Children with MS have also increased frequency of DR2(15) with RR=2.32, P=0.02 for comparison with healthy controls (Table 2) and RR=5.25, P=0.013 for comparison of the

Table 2 Phenotypic frequency of DR2(15) and several TNFa alleles in children with MS, adult MS patients and controls from the Russian ethnic group

Genetic markers	*MS with onset at age before 16 years*	*Adult MS patients*	*Controls*
DR2(15)	18 from 42 (42.9%) RR=2.32, P=0.02	68 from 167 (40.7%) RR=2.13, P<0.001	63 from 258 (24.4%)
TNFa1	1 from 27 (3.7%) n.s.	9 from 149 (6.0%) RR=18.9, P<0.001	1 from 295 (0.3%)
TNFa7	7 from 27 (25.9%) n.s.	11 from 149 (7.4%) RR=0.15, P<0.001	101 from 295 (34.2%)
TNFa9	1 from 27 (3.7%) n.s.	29 from 149 (19.5%) RR=8.66, P<0.001	8 from 295 (2.7%)
TNFa11	14 from 27 (51.9%) RR=2.45, P=0.04	36 from 149 (24.2%) n.s.	90 from 295 (30.5%)

RR, relative risk; n.s., not significant

frequencies of transmitted and non-transmitted haplotypes in familial study (Table 3).

Only one child has TNF-a1 allele – very rare in controls and more frequent in adult MS patients. Children with MS do not have increase in TNF-a9 frequency, seen in this ethnic group in adult patients (Table 2), while the frequency of TNF-a11 is significantly increased. Also children with MS have more frequent TNF-a7 allele, rare in adult patients. The frequency of TNF-a7 in children with MS is close to that observed in healthy controls – the comparison with adult MS patients showed a statistically significant difference with RR=4.39, P=0.01. Analyses of the frequencies of transmitted (MS patients) and non-transmitted haplotypes ('controls') proved the association of childhood MS with TNF-a11 (Table 3). The frequency of TNF-a7 in children with MS was two times lower than in non-transmitted haplotypes from their healthy parents (RR=0.29), while this difference does not reach statistical significance. Thus, the presence of TNF-a7 beside DR2(15) and TNF-a11 (the last two markers may be linked, Roth 1994) could be proposed as a marker of an early clinical manifestations of MS. It might be associated with a less severe MS clinical course, shown in our previous study (Gusev *et al*, 1997a). The association of these markers with clinical features of childhood MS as well as a possible association between DR and TNF markers in children with MS merits further investigations.

Table 3 Frequencies of DR2(15) and several TNFa alleles in transmitted and not-transmitted to children with MS haplotypes from their healthy parents

Genetic markers	*Transmitted haplotypes*	*Non-transmitted haplotypes*	*RR and* P-*value*
DR2(15)	14 from 34 (41.2%)	4 from 34 (11.8%)	5.25, P=0.013
TNFa1	1 from 24 (4.2%)	0 from 24 (0%)	n.s.
TNFa7	7 from 24 (29.2%)	14 from 24 (4.2%)	n.s.
TNFa9	1 from 24 (4.2%)	1 from 24 (4.2%)	n.s.
TNFa11	14 from 24 (58.3%)	5 from 24 (20.8%)	5.32, P=0.018

RR, relative risk; n.s., not significant

Materials and methods

Data from 47 children with clinically proven MS according to Poser criteria were included (26 girls and 21 boys, mean age at onset of MS 11.46 ± 0.41). Complex observation included neurological and ophthalmologic observation with perimetry, contrastometry, visual evoked potentials and MRI. Forty-two children participated in the genetic study. HLA-DRB1-typing were performed using a variant of Sequence Specific Primers (SSP) technique (Alekseev *et al*, 1995). The used set of primers allows amplification of all currently reported DRB1 alleles and to break them down into groups corresponding to DR specifities. Analysis of the length of polymorphisms in two closely linked microsatellites near TNF genes was also carried out (Nedospasov *et al*, 1991). Two-step amplification procedure provides a way to define distinct alleles of TNF-a and TNF-b alleles simultaneously with TNF-ab haplotypes. The data received were comparable with: (i) previously received data for healthy controls from the same ethnic group (328 for DRB1 and 295 for TNF; (ii) previously received data from adult MS patients (258 for DRB1 and 149 for TNF (see in Boiko, 1997; Sudomoina *et al*, 1998); and (iii) data of healthy parents of these children (34 pairs for DRB1 and 24 for TNF). Phenotypic frequencies were compared for population studies. Analyses of frequencies of transmitted and non-transmitted haplotypes were used for familial study (see Roth *et al*, 1994). Not one parent of children with MS had MS or any neurological dsyfunction suspected of being MS. Relative risk with its confidential intervals was analyses, its significance was calculated according to the χ^2-ratio with Yates correction or to Fisher two-side test.

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References

Alekseev L, Boldireva M, Trophimov D *et al* (1995). New varient of SSP technique for clinical application. *Eur J Immunogenet* **22:** 99.

Baidina TV, Shutov AA (1990). Multiple sclerosis in children. *Zh Nevropatol Psikhiatr Im S S Korsakova* **8:** 36 – 38 (in Russian).

Boiko AN (1994). Multiple sclerosis prevalence in Russia and other countries of the former USSR. In: *Multiple Sclerosis in Europe. An Epidemiological Update*. Firnhaber W, Lauer K (eds). Leuchtturm-Verlag/LTV Press, pp. 219 – 230.

Boiko A, Deomina T, Gusev E, Favorova O, Sudomoina M, Turetskaya R. (1995). Epidemiology of multiple sclerosis in Russia and other countries of the former Soviat Union: investigations of environmental and genetic factors. *Acta Neurol Scand 91* **161** (Suppl): 71–76.

Boiko AN (1997). Environmental and genetic risk factors and their role in etiology, immunopathogenesis and clinical peculiarities of multiple sclerosis. Thesis for the D.Sci. Degree, Moscow, pp 10–50 (in Russian).

Duquette P, Murray TI, Pleines I, Ebers GC, Sadovnick D, Weldon P, Warren S, Paty DW, Upton A, Hader W. (1987). Multiple sclerosis in childhood: clinical profile in 125 patients. *J Pediatrics* **111:** 359–363.

Efirmenko VN, Evtushenko SK, Chodakovskyi AV (1995). HLA-antigens in children with demyelinating diseases. *Urk Vestnik Psychonev* **3:** 177–178 (in Ukranian).

Golden GS, Woody RC (1987). The role of nuclear magnetic resonance imaging in the diagnosis of MS in childhood. *Neurology* **37:** 689–693.

Guilhoto LM, Osorio CA, Machado LR, de Castro CP, Manreza ML, Callegaro D, Kok F, Diament A. (1995). Pediatric multiple sclerosis: report of 14 cases. *Brain Develop* **17:** 9–12.

Gusev EI, Sudomoina MA, Boiko AN, Deomina TL, Favorova OO. (1997a). TNF gene polymorphisms: association with multiple sclerosis susceptibility and severity. In: *Frontiers in Multiple Sclerosis: Clinical research and therapy*. Abramsky O and Ovadia J (eds). Martin Dunitz Publishers: London pp. 35–41.

Gusev E, Sudomoina M, Boiko A, Vartdal F, Spurkland A, Nyland H, Myhr K-M, Deomina T, Turetskaya R, Favorova. O. (1997b). TNFa1 allele is associated with multiple sclerosis both in Russian and Norwegian caucasians. *J Neurol Sci* **150** (Suppl): S250.

Guseva ME (1994). Multiple sclerosis prevalence in Russia and other countries of the former USSR. In: *Multiple Sclerosis In Europe. An Epidemiological Update*. Firnhaber W, Lauer K (eds). Leuchtturm-Verlag/LTV Press, pp: 231–235.

Hanefeld F, Bauer HI, Christen HI, Kruse B, Bruhn H, Frahm J. (1991). Multiple sclerosis in childhod: report of 15 cases. *Brain Develop* **13:** 410–416.

Hanefeld F (1998). Management of multiple sclerosis in children. *Europ J Neurology* **5** (Suppl 2): S29–S30.

Hauser SL, Bresnan MI, Reinherz EL, Weiner HL (1982). Childhood multiple sclerosis: clinical features and demonstration of changes in T-cell subsets with disease activity. *Ann Neurol* **11:** 463–468.

Izquierdo G, Lyon-Caen O, Marteau R, Rartinez-Parra, Lhermitte F, Castaigne P, Hauw JJ. (1986). Early onset multiple sclerosis. Clinical study of 12 pathologically proven cases. *Acta Neurol Scand* **73:** 493–497.

Van Lieshout HB, van Engelen BG, Sanders EA, Renier WO (1993). Diagnostic multiple sclerosis in childhood. *Acta Neurol Scand* **88:** 339–343.

Nedospasov SA, Udalova IA, Kurash DV, Turetskaya RL. (1991). DNA sequence polymorphism at the human tumor necrosis factor (TNF) locus. Numerous TNF/lymphotoxin alleles tagged by two closely linked microsatellites in the upstream region of the lymphotoxin (TNF-β) gene. *J Immunol* **147:** 1053–1059.

Ohlenbusch A, Wilichowski E, Hanefeld F (1997). Characterization of the mitochondrial genome in childhood multiple sclerosis. I. Optic neuritis and LHON mutations. *Neuropediatrics* **29:** 175–179.

Ohlenbusch A, Wilichowski E, Hanefeld F (1998). Characterization of the mitochondrial genome in childhood multiple sclerosis. III. Multiple sclerosis with optic neuritis and the non-LHON-associated genes. *Neuropediatrics* **29:** 313–219.

Roth MP, Nogueira L, Coppin H, Clanet M, Clayton J, Cambon-Thomsen A. (1994). Tumor necrosis factor polymorphisms in multiple sclerosis: No additional association independent of HLA. *J Neuroimmunol* **51:** 93–99.

Sudomonia MA, Boiko AN, Demina TL, Gusev EL, Boldyreva MN, Trofimov DY, Alekseev LP, Favorova OO. (1998). Association of multiple sclerosis in the Russian population with HLA-DRB1 gene alleles. *Molecular Biol* **32:** 291–296.

Wilichowski E, Ohlenbusch A, Hanefeld F (1998). Characterization of the mitochondrial genome in childhood multiple sclerosis. II. Multiple sclerosis with optic neuritis and LHON-associated genes. *Neuropediatrics* **29:** 307–312.