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CSF characteristics in early-onset multiple sclerosis

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Abstract—The authors studied CSF characteristics in 136 patients with multiple sclerosis (MS) with a disease onset before age 16. In the initial diagnostic lumbar puncture, CSF-pleocytosis was observed in 66%, blood–CSF barrier dysfunction in 13%, and oligoclonal IgG in 92% of the early-onset MS (EOMS) patients. CSF oligoclonal IgG supports the early diagnosis of MS in childhood with a sensitivity similar to adult-onset MS.

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Compared to adult-onset multiple sclerosis (MS), early-onset MS (EOMS) causes greater diagnostic difficulties due to the age-related higher frequency of acute disseminated encephalomyelitis (ADEM) and neurometabolic white matter diseases. Recommended diagnostic criteria for MS include evidence of intrathecal IgG synthesis for a diagnosis after the first attack.^{1,2} We sought to investigate the CSF patterns of childhood MS to identify a tool for early diagnosis.

Methods and patients. *Patients.* The EOMS group contained 136 patients (85 girls, 51 boys, ratio 1.7:1) with MS onset before age 16. Median age at MS onset was 12.7 years (range 4 to 15 years). All patients were part of a larger, prospectively studied cohort of children with suspected MS admitted to our department between 1987 and 2003.³ Diagnosis of MS was established after the second attack according to the Poser criteria¹ for clinically definite MS regardless of the presence of intrathecal IgG synthesis. The initial spinal tap was performed during the first attack in 106 (78%), the second in 26 (19%), and the third in 3 (2%) patients.

The control group contained 136 age-matched patients undergoing lumbar puncture for exclusion of acute inflammatory or neurometabolic CNS diseases.

The adult-onset MS data already published in detail⁴ originate from 267 patients with clinically definite MS.¹

Methods. Albumin and IgX (G, A, M) were analyzed by standard immunochemical nephelometry. Data were evaluated numerically and graphically in CSF/serum quotient diagrams.⁵ The intrathecal, locally synthesized contribution of IgX in CSF was calculated as relative intrathecal fraction IgX_{IF} (%).⁵ Detection of oligoclonal IgG was performed by immunoblot after isoelectric focusing.⁶

Results. *Cellular immune response.* Leukocyte counts at time of first lumbar puncture, available for 121 EOMS patients, were in the range of 0 to 61/ μ L (median 8/ μ L). A total of 66% of the patients showed generally mild CSF-pleocytosis. There were no significant differences compared to adult-onset MS patients (table 1).

Blood–CSF barrier function. Protein content. Total CSF protein, available for 111 EOMS patients, was in the range of 100 to 720 mg/L (median 310 mg/L). The controls

showed CSF protein in the range of 130 to 450 mg/L (median 260 mg/L).

Albumin CSF/serum quotient. Albumin concentrations in CSF and serum were determined in 75 EOMS patients (table 2). A total of 65 patients (87%) showed an age-related normal blood–CSF barrier function (albumin CSF/serum quotient, $Q_{Aib} < 5 \times 10^{-3}$). The median Q_{Aib} was 3.7×10^{-3} (range 1.7 to 7.5×10^{-3}). The controls had a median Q_{Aib} of 3.1×10^{-3} (range 1.5 to 4.9×10^{-3}).

Intrathecal IgG synthesis. Data on intrathecal IgG synthesis were available for all 136 EOMS patients. A total of 125 patients (92%) showed CSF oligoclonal IgG when first analyzed. This intrathecal antibody production was detectable in only 69% of the patients via an increased CSF IgG fraction. Of the 11 patients initially lacking evidence of intrathecal IgG synthesis, oligoclonal bands were detectable in eight patients in a second CSF analysis performed in seven of them after the following attack, and in one patient after another three attacks. A subgroup analysis of children with a disease onset before age 10 ($n = 25$) revealed oligoclonal IgG in 96% ($n = 24$) in the first analysis, and after a second spinal tap oligoclonal IgG was detected in all patients.

Intrathecal IgA and IgM synthesis. CSF and serum IgA and IgM concentrations were analyzed in 72 EOMS patients. Intrathecal IgA synthesis was detectable in 4 (6%), intrathecal IgM synthesis in 26 patients (36%). In comparison to adult-onset MS patients, intrathecal IgM response was more frequent ($p = 0.004$), whereas the frequencies for IgG and IgA did not differ significantly.

Discussion. CSF analysis to rule out acute inflammatory and neurometabolic diseases and to find evidence for a chronic CNS immune reaction is an important tool in supporting the diagnosis of MS.

In our EOMS cohort mild CSF pleocytosis was a common finding, whereas no patients had cell counts higher than 61 cells/ μ L. A marked pleocytosis as well as a severe blood–CSF barrier dysfunction

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Table 1 Frequency of CSF leukocyte counts in patients with early-onset MS (EOMS, *n* = 121) and adult-onset MS (AOMS, *n* = 267)

Leukocytes/ μ L	EOMS	AOMS
0–4	34	43
5–9	25	26
10–14	11	13
15–24	16	11
25–34	7	4
>34	7	4

Values are percentages.

should consequently lead to a broad search for other diagnoses than MS.

CSF oligoclonal IgG is found in 98% of adult MS patients⁴ and therefore represents a sensitive diagnostic tool. Previous data on intrathecal IgG synthesis in childhood MS, confined to evaluations of less than 50 patients, were pointing to a lower prevalence.^{7,8} None of these studies focused on CSF findings and some still included patients of the pre-MRI era, calling into question both the accuracy of the methods of CSF examination and of the diagnosis of MS. Nevertheless, the largest cohort so far published contained CSF data of 47 EOMS patients and showed intrathecal IgG synthesis in 87%,⁷ only slightly below the 92% value of our cohort for the first diagnostic puncture. Whether our finding of a second lumbar puncture resulting in a frequency of 98% CSF oligoclonal IgG points to a delayed development of an oligoclonal immune response in some EOMS patients remains to be elucidated by further longitudinal studies.

An age-related increase of the prevalence of intrathecal IgG synthesis was suggested by a report describing 39 MS patients with a disease onset before age 6, as only in 8% of these patients was CSF oligoclonal IgG detected.⁸ In our MS cohort, the subgroup analysis of 25 patients with a disease onset before age 10 revealed that 24 (96%) already showed oligoclonal IgG in their first CSF analysis. However, since our study contained only one patient with a disease onset earlier than age 6, we cannot exclude that there might be different findings in very-early-onset MS.

The detection of intrathecal IgG synthesis by the

Table 2 Frequency of CSF findings in early-onset MS (EOMS) and adult-onset MS (AOMS)

	EOMS	AOMS
Oligoclonal IgG	92	98
Normal blood–CSF barrier*	87	88
Intrathecal IgG fraction >10%	69	72
Pleocytosis, >4/ μ L	66	58

Values are percentages.

* EOMS: Qalb <5 \times 10⁻³, AOMS: Qalb <7 \times 10⁻³.

merely quantitative method of intrathecal IgG fraction determination had a sensitivity of only 69% in our EOMS patients. Hence, without the qualitative analysis of oligoclonal IgG, in nearly every third child evidence for intrathecal IgG synthesis would have been missed. Moreover, quantitative assessment of intrathecal IgG synthesis by calculation of the IgG index can give false positive results with low albumin quotients, frequently observed in children.⁵ We recommend analysis of CSF oligoclonal IgG as state of the art diagnostics in every child with suspected MS.

In comparison to adult-onset MS, we found a significantly increased frequency of intrathecal IgM synthesis. Intrathecal IgM synthesis is supposed to be an unfavorable prognostic marker in adult-onset MS, reported to be associated with an earlier onset of secondary progressive disease and faster development of marked disability.⁹ Whether our subgroup of EOMS patients with intrathecal IgM synthesis develops a more rapid disease course than the remaining non-IgM EOMS patients will be the subject of a follow-up study.

One of the most frequently considered differential diagnoses of MS in childhood is ADEM. Clinical and neuroradiologic features do not permit discrimination between the two diseases at the first presentation. Remarkably, in the largest cohort of pediatric ADEM patients so far published, none of the patients in whom CSF analysis was performed (*n* = 54) had intrathecal oligoclonal IgG synthesis.¹⁰ Based on our findings of a 92% frequency for CSF oligoclonal IgG in EOMS patients, CSF analysis with detection of oligoclonal IgG might contribute substantially to an early diagnosis of MS vs ADEM. Vice versa, the absence of CSF oligoclonal IgG in a child with a supposed diagnosis of MS should lead to a detailed search for other diseases that can mimic MS (e.g., ADEM, neurometabolic disorders).

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