Oligoclonal Bands Predict Multiple Sclerosis in Children with Optic Neuritis

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We retrospectively evaluated predictors of conversion to multiple sclerosis (MS) in 357 children with isolated optic neuritis (ON) as a first demyelinating event who had a median follow-up of 4.0 years. Multiple Cox proportional-hazards regressions revealed abnormal cranial magnet resonance imaging (cMRI; hazard ratio [HR] = 5.94, 95% confidence interval [CI] = 3.39–10.39, $p < 0.001$), presence of cerebrospinal fluid immunoglobulin G oligoclonal bands (OCB; HR = 3.69, 95% CI = 2.32–5.86, $p < 0.001$), and age (HR = 1.08 per year of age, 95% CI = 1.02–1.13, $p = 0.003$) as independent predictors of conversion, whereas sex and laterality (unilateral vs bilateral) had no influence. Combined cMRI and OCB positivity indicated a 26.84-fold higher HR for developing MS compared to double negativity (95% CI = 12.26−58.74, $p < 0.001$). Accordingly, cerebrospinal fluid analysis may supplement cMRI to determine the risk of MS in children with isolated ON.

Pediatric inflammatory demyelinating optic neuritis (ON) is a rare disease with an estimated annual incidence of only 0.2/100,000.[1,2] It may remain a single

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episode or mark the clinical beginning of multiple sclerosis (MS).[3] In adults, the benefit of early onset secondary prophylactic immunotherapy in patients with clinically isolated syndrome (CIS), that is, a first episode suggestive of MS, has been established by a number of well-controlled clinical trials.[4] Comparable evidence is currently lacking in children with CIS. Furthermore, robust medication safety data are not available for this vulnerable population. Hence, prognostic indicators of the conversion risk are particularly important for secondary prophylactic treatment decisions in children.

A meta-analysis of 14 observational studies, pooling data from a total of 223 children with isolated ON as a CIS, identified higher age at presentation (for every 1-year increase in age odds ratio [OR] = 1.3, 95% confidence interval [CI] = 1.1–1.6, $p = 0.005$; adjusted for the presence of cranial magnet resonance imaging [cMRI] lesions) and a cMRI scan showing MS-compatible abnormalities outside the visual system (OR = 28.0, 95% CI = 6.3–125.1, $p < 0.001$; adjusted for age) as independent predictors of conversion to MS.[5] In contrast, the prognostic value of cerebrospinal fluid (CSF) findings in children with isolated ON is not yet clear. Pohl et al demonstrated that CSF immunoglobulin G (IgG) oligoclonal bands (OCB) were present in the large majority of investigated children with clinically definite MS already at the time of CIS, whereas CSF data for children with CIS who later did not develop MS were not reported by this study.[6] A recent retrospective study in 34 children with isolated ON indicated a potential prognostic value of CSF IgG OCB that, however, was not statistically significant in an adjusted analysis.[7]

To clarify prognostic indicators of conversion to MS in children with isolated ON as a first demyelinating event, we undertook this unprecedented retrospective multicenter approach including 357 children, treated at 27 different hospitals.

Patients and Methods

Ethics Statement

The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Würzburg (53/14). Informed consent of patients and/or their legal guardians was not required for this anonymized retrospective study. All centers informed their local data protection officers about their study participation, as recommended by the Würzburg Ethics Committee.

Patient Characteristics

Patients aged <18 years with a hospital stay for isolated ON as a first demyelinating event between 1990 and 2012 were eligible for study inclusion, with the exception of patients who had a follow-up time of <2 years and who did not develop MS within this time period. All patients had isolated typical clinical symptoms of unilateral or bilateral ON including visual loss, impairment of color vision, and eye pain on movement. Assessment of visually evoked potentials and/or coronal orbital MRI sequences were not required for study inclusion but could support the diagnosis. Bilateral ON was defined as simultaneous ON of both optic nerves or sequential bilateral ON within 4 weeks apart. All patients received a cMRI scan and an evaluation of CSF IgG OCB by isoelectric focusing with IgG immunoblotting or silver staining as part of the routine diagnostic workup. All children had additional laboratory investigations to exclude differential diagnoses such as neuroborreliosis. Abnormal cMRI, as assessed by the neuropediatricians contributing to this study, was defined by at least 1 MS-compatible lesion with a diameter of >3mm located outside the optical nerves and chiasm. No standardized MRI protocol was used in this retrospective study. Positive for OCB was defined as ≥2 CSF bands not detected in the serum. Collected information included sex, age at presentation with isolated ON, laterality (unilateral vs bilateral), corrected visual acuities of affected eyes at presentation, cMRI status at presentation (normal vs abnormal), CSF OCB at presentation (negative vs positive), start of immunomodulatory treatment after ON, length of follow-up, time to MS development in the MS group, and diagnosis at the end of follow-up. MS was diagnosed according to the so-called McDonald 2010 diagnostic criteria, not necessarily requiring a second clinical event but instead allowing demonstration of dissemination in space and time on MRI for a diagnosis of MS.[8] Follow-up investigations were routinely practiced by all participating centers, although they did not follow a standardized protocol. Thirty-four patients (9.5% of the total cohort) were previously reported separately using different statistical methodology,[7] whereas data for the remaining 323 patients was not previously available.

Statistical Analyses

Descriptive statistics were calculated using Prism 5 software (GraphPad, La Jolla, CA). To assess MS risk factors, simple and multiple Cox proportional-hazards regressions were performed (survival analyses). In the univariate analyses, we examined the effects of age, sex, positive cMRI, positive OCB (the latter 2 alone or in combination), and laterality on diagnosis (MS compared to no MS). We ran 2 multiple regression analyses in which we investigated the effects of positive cMRI and OCB, controlling for ON type, age, and sex. In the first model, cMRI and OCB were included as binary covariates (we also examined their interaction in a separate model, but its effect was small and nonsignificant); in the second model, we included a categorical variable comprising information from both cMRI and OCB (none positive, 1 positive, both positive) in an attempt to overcome their strong correlation (tetrachoric rho = 0.765). All regressions were executed in bootstraps of 1,000 repetitions, an approach that does not make assumptions regarding the distribution of the estimated statistics and allows more precise standard error estimates than the standard analyses, thus providing more reliable confidence intervals and p-values. Additionally, we used logistic regressions to quantify the predictive strength of

TABLE 1. Characterization of Patients according to Diagnostic Status at End of Follow-up

Characteristic	No MS[a]	MS[b]	Total
Patients, No.	212	145	357
Median age at onset, yr, (IQR, range)	12.7 (9.7–15.0, 2.8–17.9)	14.7 (12.9–16.1, 4.3–17.9)	13.6 (10.8–15.5, 2.8–17.9)
Female [%]	142 [67.0]	101 [69.7]	243 [68.1]
Median corrected visual acuities of affected eyes (IQR, range)	0.6 (0.2–0.8, 0–1.5)	0.4 (0.1–0.8, 0–1.0)	0.5 (0.2–0.8, 0–1.5)
Median time to MS development, yr (IQR, range)	n.a.	0.7 (0.3–1.3, 0.1–5.0)	n.a.
Median follow-up, yr (IQR, range)	4.2 (2.8–6.2, 2.0–22.0)	3.3 (2.0–6.3, 0.3–22.0)	4.0 (2.4–6.2, 0.3–22.0)
Bilateral ON [%]	51 [24.1]	22 [15.2]	73 [20.4]
cMRI abnormal [%]	36 [17.0]	126 [86.9]	162 [45.4]
CSF OCB positive [%]	32 [15.1]	117 [80.7]	149 [41.7]
Both cMRI abnormal and CSF OCB positive [%]	9 [4.2]	107 [73.8]	116 [32.5]
Immunomodulatory treatment after ON [%]	20 [9.4]	75 [51.7]	95 [26.6]

[a]Follow-up time varied between 2 and 22 years (mean = 5.7, median = 4.2).
[b]Time until diagnosis varied between 0.1 and 5 years (mean = 1.0, median = 0.7).
cMRI = cranial magnet resonance imaging; CSF = cerebrospinal fluid; IQR = interquartile range; MS = multiple sclerosis; n.a. = not applicable; OCB = oligoclonal bands; ON = optic neuritis.

cMRI, OCB, and both on 2-year, 3-year, and 4-year conversion to MS, and to calculate the area under the curve (AUC) for these models. An α level of 0.05 and Stata v12.1 (StataCorp, College Station, TX) were used for all analyses, which were based on a priori decisions, and we did not analyze any other variables not reported here.

Results

In total, 357 children with isolated ON were included, of whom 40.6% had MS by the end of a median follow-up of 4.0 years. In the non-MS group (n = 212), 167 children were finally diagnosed with single isolated ON, 40 with recurrent isolated ON, and 5 with neuromyelitis optica.[9] Demographic data and results of investigations, stratified by diagnostic status at the end of follow-up (no MS vs MS), are provided in Table 1. As shown in this table, patients who later developed MS were much more likely to start immunomodulatory therapy after their first clinical event due to the presence of MS risk factors, as previously established in adults and partially in children.

Univariate Cox proportional-hazards regressions indicated higher age, abnormal cMRI, and presence of CSF IgG OCB but not ON laterality or sex as predictors of conversion to MS. Combined cMRI and OCB positivity showed a higher predictive value than each of the factors alone (Table 2). A multivariate analysis demonstrated age, abnormal cMRI, and OCB positivity as independent predictors of conversion, whereas sex and laterality had no effect. The second multivariate analysis, which included positivity of either cMRI or CSF, positivity of both cMRI and CSF, laterality, age, and sex, demonstrated that for patients with both a pathological cMRI scan and detection of OCB at presentation, the hazard ratio (HR) for developing MS was >20 times higher than the HR for patients with positivity of neither cMRI nor CSF.

In addition, multiple logistic regressions used to calculate AUCs confirmed a high sensitivity and specificity of cMRI and CSF investigations in determining the risk of conversion to MS within 2, 3, and 4 years, with the combination of both factors showing the highest predictive value for all time points (Fig). Focusing on 4-year conversion risk in patients who had a minimum follow-up time of 4 years (n = 291), we observed 143 MS and 148 no MS cases, and the following distributions of cMRI and CSF findings. Among the 150 cMRI-positive

TABLE 2. Factors Influencing the Risk of Conversion to Multiple Sclerosis after Isolated Optic Neuritis: Results of Cox Proportional-Hazards Regressions (Survival Analyses) Including Bootstrap Simulations with 1,000 Repetitions, N = 357

Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI	*p*
Univariate analysis[a]				
Sex (female)	1.12	0.80	1.55	0.512
Age (per year of age)	1.15	1.10	1.22	<0.001
Laterality (bilateral)	0.67	0.43	1.03	0.067
cMRI (abnormal)	11.53	7.02	18.95	<0.001
CSF OCB (positive)	8.07	5.38	12.11	<0.001
cMRI (abnormal) and CSF OCB (positive)	28.91	14.21	58.79	<0.001
Multiple regression analysis 1, analyzing cMRI and CSF as separate factors[b]				
Sex (female)	0.95	0.74	1.23	0.701
Age (per year of age)	1.08	1.02	1.13	0.003
Laterality (bilateral)	1.15	0.80	1.64	0.447
cMRI (abnormal)	5.94	3.39	10.39	<0.001
CSF OCB (positive)	3.69	2.32	5.86	<0.001
Multiple regression analysis 2, analyzing the combined predictive value of cMRI and CSF[b]				
Sex (female)	0.94	0.72	1.24	0.669
Age (per year of age)	1.08	1.03	1.14	0.003
Laterality (bilateral)	1.14	0.79	1.64	0.495
cMRI CSF OCB (1 positive)	7.52	3.25	17.41	<0.001
cMRI CSF OCB (both positive)	26.84	12.26	58.74	<0.001

[a]The inclusion of these variables was based on an a priori decision, and we did not analyze any other variables.
[b]Analyses included 356 of the 357 patients, because OCB information was missing for 1 patient.
CI = confidence interval; cMRI = cranial magnet resonance imaging; CSF = cerebrospinal fluid; OCB = oligoclonal bands.

patients, only 18 of 37 OCB-negative patients (49%) developed MS, whereas 107 of 113 OCB-positive patients (95%) did so. Among 141 patients with a negative cMRI scan, 9 of 115 OCB-negative patients (8%) and 9 of 26 OCB-positive patients (35%) developed MS within 4 years. Of note, only 5 of 40 children with a final diagnosis of recurrent isolated ON (12.5%) and none of 5 children with neuromyelitis optica had CSF OCB during their first clinical episode.

Discussion

This retrospective observational multicenter study in 357 children with isolated ON as a first demyelinating event newly defined the presence of CSF-restricted IgG OCB at clinical onset as an independent risk factor for the development of MS. It confirmed a pathological cMRI scan as a strong independent predictor and higher age at onset as a weaker independent predictor of conversion to MS. Combined positivity of cMRI and CSF revealed a higher prognostic power than both of these closely correlated factors alone, as previously reported in adults.[10,11] CSF OCB at onset were infrequent in children with recurrent isolated ON and not observed in those few patients with neuromyelitis optica. Accordingly, the authors think that CSF analysis should be considered as part of the routine diagnostic workup in children with isolated ON, as it will not only help to exclude differential diagnoses such as infections[12]; moreover, it may supplement cMRI in the prognostic evaluation regarding conversion to MS and thereby inform secondary prophylactic treatment decisions.

Previous studies identified higher age at onset as a risk factor for the development of MS.[5] Higher age was confirmed as an independent risk factor in our cohort in multivariate analyses; however, it had a comparatively

weak predictive value, with an HR of 1.08 per year of age. Accordingly, careful clinical and cMRI follow-up investigations need to be considered for younger as well as older children with isolated ON. Of note, 69.7% of the children developing MS within our cohort did so within the first year after ON, highlighting the particular importance of early vigilance.

Previous smaller observational studies had identified unilateral[7,13–15] and others bilateral[3,16] pediatric ON as a risk factor for the development of MS. In line with a recent meta-analysis of smaller observational studies,[5] laterality of ON did not exhibit prognostic value regarding the conversion to MS in our cohort, not only in multivariate analyses but also in a less robust but more sensitive univariate analysis, where only borderline significance was observed for a lower risk after bilateral ON. This is in contrast to findings in adults, where bilateral as compared to unilateral ON is associated with a much lower risk of conversion to MS.[17]

Interestingly, we observed a higher MS conversion rate of 40.6% compared to earlier pediatric studies reporting conversion rates between 0 and 30%.[18] The rate was higher despite the start of immunomodulatory treatment in 26.6% of our children with isolated ON. Such treatment was shown to decrease the rate of conversion to MS in adults with CIS and may have biased our results toward less MS cases compared to a natural history cohort.[4] The use of more sensitive diagnostic criteria for MS in our cohort and a potential selection bias for MS versus non-MS patients by an allowed shorter minimum follow-up period for future MS patients may partially explain the difference to previous studies. However, a median follow-up of 4.2 years in the non-MS group, which is longer than in many previous pediatric studies,[15] might argue against the latter point. Instead, the observed lower rate of children with bilateral optic neuritis (20.4%) as compared to previously reported rates (33–86%)[18] might point toward a change in the natural history of pediatric optic neuritis, bringing it closer to adult ON, where the MS conversion rate is higher and bilateral ON is less frequent than in children.[17]

This study is mainly limited by its retrospective observational design, which may have biased the results. Follow-up investigations were not standardized. MRI scans were evaluated for this study by neuropediatricians, not neuroradiologists. Furthermore, not all information of potential predictive relevance was collected in favor of

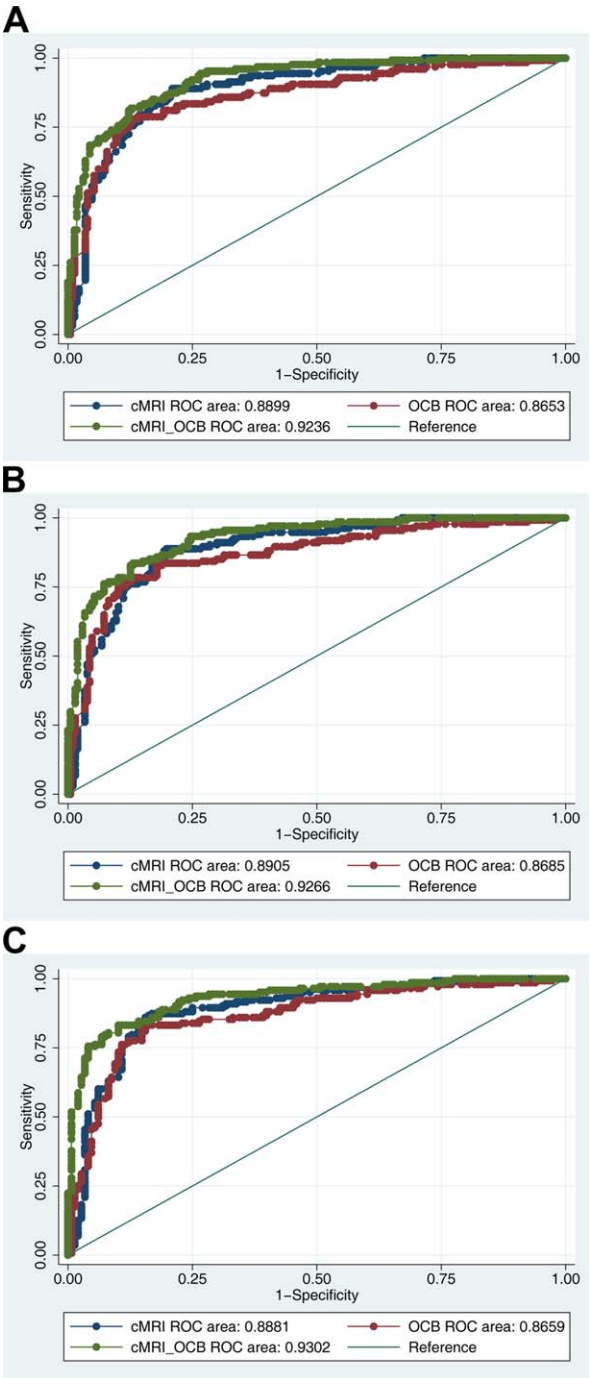

FIGURE : Explanatory power of multiple logistic regression models for conversion to multiple sclerosis (MS) within 2, 3, and 4 years. Multiple logistic regressions were used to calculate areas under receiver operating characteristic (ROC) curves (AUCs). Per protocol, all non-MS patients had a minimum follow-up of 2 years. For the 3- and 4-year analysis, only non-MS patients with a minimum follow-up of 3 or 4 years, respectively, were included. (A) Two-year conversion risk for 356 patients: cranial magnet resonance imaging (cMRI; AUC = 0.890, 95% confidence interval [CI] = 0.855–0.925), oligoclonal bands (OCB; AUC = 0.865, 95% CI = 0.823–0.907), both (AUC = 0.924, 95% CI = 0.896–0.951). (B) Three-year conversion risk for 341 patients: cMRI (AUC = 0.891, 95% CI = 0.856–0.926), OCB (AUC = 0.869, 95% CI = 0.827–0.910), both (AUC = 0.927, 95% CI = 0.899–0.954). (C) Four-year conversion risk for 291 patients: cMRI (AUC = 0.888, 95% CI = 0.848–0.928), OCB (AUC = 0.866, 95% CI = 0.823–0.909), both (AUC = 0.930, 95% CI = 0.901–0.959).

a simple design and a complete data set for each patient. The authors do not think that the restriction to hospitalized patients, potentially enriching for patients with more severe ON, introduced a major bias. First, our cohort included many patients with mild ON (see visual acuities in Table 1); second, German diagnostic guidelines did and do recommend CSF analysis as a standard procedure in patients with CIS, and CSF analysis in children is usually done during a hospital stay. It should be noted as a limitation that the calculated AUCs will be overly optimistic because they were only calculated for the patients on whom the model was developed. Validation with an independent second sample would be required for a more accurate quantification of the predictive power of the model, especially if it is to be further developed as a risk-prediction tool. The main strengths of this study lie in its unprecedented cohort size, enabling a rigorous statistical approach, and in its multicentricity, with 27 participating centers, increasing the robustness of the results. Accordingly, this work represents an important step forward in the characterization of prognostic indicators in children with isolated ON and it will help to guide prognostic evaluation and treatment decisions.

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Authorship

N.H.: study conception and design, study coordination, data acquisition and analysis, edited the manuscript; E.K.: statistical analyses, edited the manuscript; J.G.-A.: data acquisition, reviewed the manuscript; A.J.: data acquisition, edited the manuscript; G.V.: data acquisition, reviewed the manuscript; R.K.: data acquisition, edited the manuscript; P.Ho.: data acquisition, reviewed the manuscript; S.M.: data acquisition, edited the manuscript; I.B.: data acquisition, reviewed the manuscript; B.K.: study conception, data acquisition, reviewed the manuscript; P.He.: data acquisition, reviewed the manuscript; M.Sc.: data acquisition, reviewed the manuscript; K.W.: data acquisition, reviewed the manuscript; M.G.H.: data acquisition, edited the manuscript; S.L.: data acquisition, reviewed the manuscript; M.K.: data acquisition, reviewed the manuscript; A.B.: data acquisition, reviewed the manuscript; M.Sm.: data acquisition, reviewed the manuscript; S.K.: data acquisition, reviewed the manuscript; M.P.: data acquisition, reviewed the manuscript; K.R.: data acquisition, edited the manuscript; T.L.: data acquisition, reviewed the manuscript; P.W.: data acquisition, reviewed the manuscript; R.T.: data acquisition, reviewed the manuscript; J.K.: data acquisition, reviewed the manuscript; M.H.: data acquisition, reviewed the manuscript; R.H.: data acquisition, reviewed the manuscript; R.W.: data acquisition, reviewed the manuscript; A.M.: data acquisition, reviewed the manuscript; M.B.: study conception and design, obtained ethics approval, study coordination, statistical analysis (descriptive statistics), drafted and edited the manuscript.

Potential Conflicts of Interest

A.J. and K.R. have nothing to disclose. COI forms for these authors were already submitted with the first version of this manuscript. We send you again the forms for Dr Jenke and Dr Rostasy together with these proof corrections.

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