Diagnostic value of oligoclonal bands in children: A nationwide population-based cohort study

Magnus S Boesen[a], Alfred P Born[a], Poul E H Jensen[b], Finn Sellebjerg[b], Morten Blinkenberg[b], Magnus C Lydolph[c], Mikala K Jørgensen[d], Lene Rosenberg[e], Jesper Q Thomassen[f], Malene L Børresen[a]

[a] Department of Pediatrics, Rigshospitalet, University of Copenhagen, Denmark
[b] Danish Multiple Sclerosis Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark
[c] Department of Autoimmunity & Biomarkers, Statens Serum Institut, Denmark
[d] Department of Clinical Biochemistry, Zealand University Hospital, Region Zealand, Denmark
[e] Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark
[f] Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Denmark

Background

Oligoclonal bands (OCBs) are electrophoretic patterns of immunoglobulins produced by plasma cells, and positive OCBs are markers of chronic central nervous system (CNS) inflammation. Pediatricians often face the dilemma of whether to examine OCBs in cerebrospinal fluid (CSF). "Positive" OCBs are particularly associated with relapsing acquired demyelinating syndromes (ADS) and are present in up to 81% of children with multiple sclerosis (MS). However, MS is rare in children, especially in children younger than 12 years of age. In contrast, the most common ADS in children is acute disseminated encephalomyelitis (ADEM), but only 0–10% of children with ADEM present with positive OCBs. In addition, ADEM can be reliably distinguished from MS based on the clinical presentation (age at onset younger than 12 years, presence of encephalopathy, and polyfocal neurological deficits) as well as MRI findings including diffuse bilateral T2 white matter lesions and lack of 'typical MS lesions'. Furthermore, only one in four children with central nervous system (CNS) infection or immune-mediated CNS diseases presents with positive OCBs. Thus, the diagnostic value of OCBs in children may be limited, particularly in children younger than 12 years of age.

Objective/hypothesis

We aimed to evaluate the diagnostic value of OCBs in children and whether the diagnostic value was age dependent. Our hypothesis was that the pathophysiology of ADS differs in children before and after age 12 years; accordingly, the predictive value of OCB positivity differs between children aged 0–11 years and children aged 12–17 years.

Methods

In a nationwide population-based setting, we retrieved data on 2,055 children's OCB examination including concordant cerebrospinal fluid biomarkers during 1994–2017. Case ascertainment was by review of medical records and diagnostic codes.

We grouped children into 'CNS diseases' and 'non-CNS diseases' (Table 1). Further, we divided CNS diseases into the following groups: ADS (e.g. ADEM, MS), non-ADS immune-mediated CNS diseases (e.g. Rasmussen's encephalitis), CNS infection (e.g. bacterial encephalitis), epilepsy, sleep disorders (e.g. narcolepsy), CNS malignancy, movement disorders (e.g. chorea, dystonia), static encephalopathy (e.g. cerebral palsy), progressive encephalopathy/mitochondrial disease (e.g. Leigh syndrome), cerebrovascular disease (e.g. stroke), or other CNS diseases (e.g. hydrocephalus, asphyxia).

We used Fisher's exact test to explore distribution differences of OCB positivity in ADS before and after 12 years of age and calculated sensitivity, specificity, positive predictive value, and negative predictive value of OCBs to distinguish ADS from the other diagnostic groups.

The study was approved by the Danish Data Protection Agency (30-1423/03567) and the Danish Health Data Authority (00003101). The Danish Health and Medicines Authority waived the requirement to obtain patient informed consent to access medical records (case number 3-3013-896/2).

Results

Among the 2,055 children included, 209 (10%) were OCB positive at the first OCB examination. Median age at OCB examination was 15.2 years (range=1.8–18.0). OCB positivity was the highest in ADS (52%) (Table 1).

Table 1. Baseline demographic and cerebrospinal fluid data by diagnostic groups

Diagnostic group	Children, n (% total)	Age at onset, y, median (range)	CSF pleocytosis, n (%)	OCB positive, n (%)
ALL DISEASES	2,055 (100%)	14.1 (0.02–18.0)	291 (22%)	209 (10%)
Non-CNS disease	933 (45%)	14.8 (0.02–18.0)	82 (13%)[e]	37 (4%)
CNS disease (subgroups below)	1,122 (55%)	13.5 (0.08–18.0)	209 (31%)	172 (15%)
ADS	211 (10%)	15.2 (1.8–18.0)	82 (63%)	109 (52%)
Other immune-mediated CNS	61 (3%)	10.2 (0.7–18.0)	16 (44%)	11 (18%)
CNS infections	143 (7%)	11.0 (0.2–17.8)	50 (69%)	18 (13%)
Epilepsy	98 (5%)	11.3 (0.3–17.7)	13 (22%)	2 (2%)
Sleep disorders	65 (3%)	15.7 (4.8–17.9)	2 (5%)	4 (6%)
Malignant	31 (2%)	11.6 (0.9–17.3)	7 (32%)	5 (16%)
Movement disorders	29 (1%)	14.6 (1.3–17.4)	1 (5%)	1 (3%)
Static encephalopathy	155 (8%)	5.6 (0.1–17.6)	8 (10%)	11 (7%)
Cerebrovascular disease	43 (2%)	14.8 (0.1–17.9)	7 (23%)	2 (5%)
Progressive encephalopathy	8 (0.4%)	8.8 (0.6–15.5)	2 (40%)	1 (13%)
Other CNS diseases	278 (14%)	14.7 (0.2–17.9)	21 (11%)	8 (3%)

However, OCB positivity in ADS was highly age-dependent: 21% were OCB positive in children with ADS before age 12 years and 68% in children 12–17 years ($p<0.0001$) due to higher incidence of multiple sclerosis in the latter. Further, in a cohort with medical-record validated ADS, 2/25 (8%) of children with ADEM and 58/62 (94%) with MS were OCB positive at presentation. In line, positive OCBs were not predictive of ADS before age 12 years compared with the other diagnostic groups. However, positive OCBs in children aged 12–17 years were highly predictive of ADS compared with CNS infections and non-ADS immune-mediated CNS diseases (positive predictive value: 0.89; 95% CI=0.82–0.94; $p<0.0001$), but negative OCBs were not discriminatory (negative predictive value: 0.35; 95% CI=0.17–0.57; $p=0.17$).

Conclusion

In a clinical setting, cerebrospinal fluid OCB examination may be diagnostically valuable only in children aged 12–17 years if there is clinical suspicion of MS, and in such circumstances only a positive test has clinically relevant predictive value.

Corresponding author:
magnus.spangsberg.boesen@regionh.dk

Disclosures

Dr. **Boesen** has served on a scientific advisory board for Teva; has received speaker honoraria for lecturing from Novartis and support for congress participation from Teva, Novartis and Roche.
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