Progressive myelin oligodendrocyte glycoprotein associated demyelination mimicking leukodystrophy.

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Abstract

Background

Myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) may be associated with relapsing disease but clinical progression independent of relapse activity is rare.

Objectives

To report progressive disease in a patient with MOGAD.

Methods

A single retrospective case report.

Results

At 4yrs of age the patient had a single episode of acute disseminated encephalomyelitis. She remained well until age 17yrs but over the next 9yrs developed progressive spastic quadriparesis, cognitive and bulbar dysfunction. Brain imaging showed a leukodystrophy-like pattern of white matter abnormality with contrast enhancement at different time points. MOG-IgG was repeatedly positive by live cell-based assay.

Conclusion

Secondary progression may be a rare presentation of MOG-IgG associated disease.

Main Text

Introduction

Myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) are a recognised biomarker in a subset of patients with central nervous system (CNS) inflammation. Typical manifestations include acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, and brainstem inflammation. Relapsing disease has been reported in 36-61% of children, but progressive disease is rare. Herein we describe a patient with a secondary progressive course, with worsening motor and cognitive disability spanning almost 10yrs.

Presentation

At age 4yrs, the patient developed acute upper and lower limb incoordination over a 3-week period. Pyramidal and cerebellar signs were noted. The brain MRI report described signal abnormality in both cerebellar hemispheres, cerebellar and cerebral peduncles, brainstem, thalami and left internal capsule (images unavailable). Cerebrospinal fluid (CSF) contained 14 white cells/mm^3, other constituents were unavailable. A diagnosis of ADEM was made. No follow-up examination or imaging was reported, but her parents (both doctors) felt she made a rapid and full recovery after a 3-day course of dexamethasone.

She subsequently commenced full time education and made good academic progress until age 17yrs, after which her school performance declined. She then developed ataxia with loss of ambulatory function for 1 week followed by spontaneous, albeit partial, resolution. MRI showed symmetrical, predominantly white matter abnormality involving the cerebral white matter and right middle cerebellar peduncle (leukodystrophy-like); (Figure A1). CSF contained WCC <1mm^3, protein 0.35g/L and negative oligoclonal bands. Visual evoked potentials demonstrated a delay in right P100 latency. Over the next 2yrs there was progressive decline in cognitive and ambulatory function. Neuropsychology assessment at age 18yrs demonstrated impaired executive function, memory, abstract reasoning, problem solving and cognitive speed. By age 19yrs she had developed bowel and bladder incontinence. Repeat neuropsychological evaluation demonstrated further deterioration in all cognitive domains.

The following tests were satisfactory; MR angiography, serum cortisol, lactate, angiotensin converting enzyme, creatinine kinase, very long chain fatty acids, arylsulfatase, white cell enzymes, plasma and urine amino acids, CSF lactate, mitochondrial mutation screen, and whole genome sequencing.

Repeat MRI brain at age 20yrs showed several contrast-enhancing lesions in the left middle cerebellar peduncle, right temporal lobe, left corona radiata and left parietal lobe (Figure A2). A 6-week course of oral prednisolone was commenced which resulted in resolution of contrast enhancement but no clinical improvement (Figure A3). Three months later she developed non-convulsive status epilepticus. Her electroencephalogram showed focal right anterior temporal region changes with prominent background slowing. Anti-seizure medication was commenced (topiramate, levetiracetam, phenytoin with clobazam as required) but her focal and generalised seizures remained refractory.

Over the next 2yrs she became progressively mute and non-ambulant requiring 24-hour care. A percutaneous endoscopic gastrostomy was inserted due to impaired swallow function. At age 23yrs optic disc pallor, mutism, and a spastic tetraplegia with minimal volitional head movement were noted. At age 21 yrs a frontal lobe biopsy was performed. The biopsy fragments included cortex, subcortical white matter and juxta-ventricular white matter. A few white matter fragments showed a degree of myelin pallor and vacuolisation (Figure A5 and A6). This was not associated with myelinophagia, neuro-inflammation, or neuro axonal spheroids. There were no features to suggest metachromasia, infection or underlying neoplasia. Around this time her serum (but not CSF) MOG-IgG returned positive (1:200) by live cell-based assay (tested by the Oxford Autoimmune Group) and further testing 3 months later was also positive (1:200). A 5-day course of methylprednisolone, 5 cycles of plasma exchange (PLEX) and maintenance prednisolone 15mg/day were administered but without significant change. Over the next 6 months several admissions were required for seizure control and Prednisolone was increased to 20mg/day.

At age 24yrs, a new right middle-superior cerebellar peduncular lesion was noted on MR brain imaging (Figure A4). Rituximab was commenced with a degree of subjective clinical stabilisation over the next 7 months. Longitudinal MR brain studies showed progressive volume loss in bilateral cerebral and

cerebellar hemispheres and the brainstem. Unfortunately, further clinical deterioration was noted 7 months and MRI brain imaging showed further areas of contrast enhancement. Aggressive escalation options including autologous stem cell transplantation were discussed, but in view of advanced disability (EDSS 9.5) the addition of regular intravenous immunoglobulin with Rituximab was agreed upon.

Discussion

Progressive cases of MOGAD are rare, with only 7 reported to date.[1-3] In this patient, the initial presentation with acute disseminated encephalomyelitis (ADEM) was in keeping with the age dependent pattern reported in other large cohorts.[4-6] In children with onset <10years, the most common MOG-IgG associated presentation is ADEM, whilst in adults optic neuritis (ON) and/or transverse myelitis (TM) predominate.[5] Interestingly, older children (10-17 years), appear to present with ADEM or isolated ON in more equal distribution, suggesting the transition from childhood to adulthood may be reflected in a changing MOGAD phenotype. However, the relentless neurological decline in this case is unusual, especially considering results from a recent French study showing better clinical outcomes in children, even those with severe index presentations.[5] Progressive neurological decline may be due to a protracted inflammatory episode, subclinical relapsing inflammatory activity, or neurodegeneration.[7,8] Based on the longitudinal decline in brain volume and contrast enhancing lesions, it is likely there was overlap between these three processes. It is also possible that refractory seizure activity contributed to the patient's cognitive decline. Interestingly a recent study of multiple sclerosis patients highlighted the loss of re-myelination capacity and reparative mechanisms with advancing age and disease duration, and may pose a possible explanation for the delayed accrual of disability in this case .[9]

In view of the progressive clinical course careful consideration was given to the diagnosis. A genetic or metabolic leukodystrophy was considered but appropriate metabolic tests and whole genome sequencing were negative. MOG-IgG was repeatedly detected (1:200) by live cell-based assay. This coupled with initial steroid responsiveness, contrast enhancing lesions and mild CSF pleocytosis favoured a neuroinflammatory rather than metabolic disease. Furthermore, the imaging was similar to

a leukodystrophy-like pattern previously reported in children with MOG-IgG, some of whom had poor responses to immunotherapy and developed long term disability.[10] In this case Rituximab initially appeared effective but this effect was not maintained. Indeed, we have observed relapses in 79% of MOGAD patients despite adequate CD19 depletion and accordingly this patient is due to commence regular intravenous immunoglobulin.[11]

Progressive cases such as this continue to expand the clinical spectrum associated with MOG-IgG and may provide insights into the pathophysiology of the disease process. MOG-IgG testing should be considered in children or adults with presumed but unproven 'leukodystrophy'.

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Disclosures/Conflict of Interests

Dr E Gibbons, Dr D Whittam, Dr K Elhadd, Dr M Bhojak, Dr N Rathi, Dr S Avula, Dr M Griffiths and Dr S Huda report no disclosures or conflict of interest.

Dr A Jacob served on the scientific advisory board for Shire Pharmaceuticals; received travel funding and/or speaker honoraria from Biogen Idec, Shire, and Terumo BCT; consulted for Shire Pharmaceuticals; and received research support from Biogen, Alexion Pharmaceuticals, NHS, and University of Liverpool.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.