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BRAINCHILD

The Official Publication of HKCNDP
Special Issue on Neuroimmunology

香港兒童腦科及體智發展學會
The Hong Kong Society of Child Neurology and Developmental Paediatrics

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The Hong Kong Society of Child Neurology & Developmental Paediatrics

EDITOR'S NOTES for the August 2020 Issue

Neuroimmunology

Dr. Kwing Wan TSUI

Recent advances showed that immunological etiology plays an important role in many neurological diseases. In this issue of BrainChild, we will present to you five excellent articles related to immune disorders of central nervous systems.

International League Against Epilepsy (ILAE) classified epilepsy into five categories, namely genetic, structural, metabolic, infectious and immune causes. Autoimmune mechanism encompasses a wide spectrum of epileptic disorders from anti-NMDAR encephalitis with known antibody identified to diseases with presumed immune etiology, such as Rasmussen encephalitis and FIRES. Dr. Richard Chang listed a number of these epileptic disorders including CNS presentation as part of the systemic autoimmune diseases. An important message is that empirical immunotherapy should be considered for better prognosis when other causes are preliminarily excluded since it may take long time to get antibody results or the test is not yet available.

Besides epileptic seizure, autoimmunity can cause a wide range of neurological presentations. Prof. Ming Lim reviewed diagnosis and management of autoimmune encephalitis with an update on recent advance of this topic. Despite the availability of antibodies testing, use of diagnostic criteria for possible autoimmune encephalitis / probable anti-NMDA receptor encephalitis as introduced by Prof. Lim would assist in early identification and treatment, which is an important factor to improve outcome. With improved recovery in patient with autoimmune encephalitis, neurocognitive sequelae was observed in significantly high proportion of cases. It was recommended in his article that early engagement to neuropsychological assessment, counselling and support during rehabilitation should be provided.

Multiple sclerosis (MS) is a well-recognized autoimmune disease causing CNS demyelination with progressive or relapsing course leading to chronic disabilities. Disease modifying agents have become the mainstay of treatment and provides promising results which change the outlook of prognosis in MS patients. In Dr. Richard Li's article, he concisely updated the recent progress of MS management in Hong Kong, in particular the catching up of medication use to reach the international standard. The Hong Kong Multiple Sclerosis Society currently under his presidency contributed significantly to both patients support and exchange of knowledge among professionals. Dr. Li also introduced advancement in other two CNS inflammatory diseases, related to ant-myelin oligodendrocyte glycoprotein (anti-MOG) antibody and anti-aquaporin-4 (AQP4) antibody, with tests currently available in Queen Mary Hospital. Other articles in this issue further elaborate details of these two entities.

MOG antibody is a relatively recent discovery and we just begin to understand its role in acquired demyelinating syndromes (ADS). Dr. Alvin Ho in his article provided a clear picture on clinical presentation of MOG associated ADS, namely acute disseminated encephalomyelitis, optic neuritis, transverse myelitis, neuromyelitis optica spectrum disorders, cortical encephalitis and brainstem attacks. He also mentioned overviews on treatment and prognosis on MOG antibody-associated diseases.

Dr. Jerry Lok and Dr. Carmen Chan provided a comprehensive review on the management of optic neuritis and an update on roles of anti-MOG and aquaporin-4 antibodies in this disorder. The treatment algorithm served as a good guidance to management of ON in both adult and paediatric age groups with emphasis on the need to look out for atypical features and consider other differential diagnoses, such as multiple sclerosis, ADEM and neuromyelitis optica spectrum disorder.

Last but not least, I would like to thank all the authors who contributed to this issue of BrainChild and members of the editorial board guest editors who spent their valuable time and efforts to make publication of this issue successful.

Dr. Kwing Wan TSUI

President
The Hong Kong Society of Child Neurology and Developmental Paediatrics

Advances in Diagnosis and Management of Autoimmune Encephalitis

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The encephalitides are a heterogeneous and clinically challenging group of conditions. Encephalitis describes inflammation of the brain parenchyma with neurological dysfunction[1] and is distinguished from encephalopathy in which neurological dysfunction is not necessarily associated with evidence of brain inflammation. Evidence of inflammation is therefore important in the diagnosis of encephalitis, yet tissue diagnosis premortem is challenging, and surrogates for brain inflammation such as MRI changes or CSF pleocytosis are present in only a proportion of patients presenting with encephalitis. Establishment of clear diagnostic criteria for a diagnosis of encephalitis remains challenging, which has implications for establishing the epidemiology, aetiology and management of encephalitis.

The differential diagnosis for a child or adult presenting with encephalitis is wide. Infective encephalitis has been recognised since the time of Hippocrates,[2] and implicated in the death of Alexander the Great.[3] However in a large proportion of cases an infective agent is never isolated. Furthermore, in a large proportion an infective trigger is recognised, which appears clinically distinct from the subsequent encephalitic illness. In these patients autoimmune encephalitis may be suspected.

A number of challenges are inherent in the diagnosis of autoimmune encephalitis. The concept of immune mediated CNS disease is wide in its scope and may be incorporate a number of pathological processes.[4] Immune-mediated disease loosely describes those conditions in which the immune system is suspected to be involved, while innate immune activation describes CNS manifestations of an activation of the innate immune system. Autoimmune disease describes an acquired immune process in which autoreactive lymphocytes or auto-antibodies target the CNS, while 'Auto-antibody associated' describes an autoimmune condition in which a potentially pathogenic auto-antibody is detected.

A number of acute neurological presentations have been associated with specific autoantibodies, some of which have been shown to be pathogenic in vitro and vivo studies. In such cases it has been possible to build a phenotype with some confidence. The detection of new auto-antibodies, such as that to Myelin Oligodendrocyte Glycoprotein (MOG) present in a large proportion of children with acute disseminated encephalomyelitis (ADEM) have allowed classification of cases with some confidence. Nonetheless, this progress emphasises the likelihood of a number of as yet unknown pathogenic autoantibodies. Therefore there are a large number of children who will present with clinical features of autoimmune disease, in whom it is not possible to confirm the presence of a pathogenic auto-antibody.

In this review we highlight recent advances in the diagnosis and management of autoimmune encephalitis, progress in our understanding of the pathology underlying autoimmune encephalitis, and clinical and research challenges that lie ahead.

Diagnosis of autoimmune encephalitis in children

A proportion of children presenting with autoimmune encephalitis may do so with features of well described syndromes such that a combination of clinical and radiological features may allow a diagnosis to be made with some confidence without antibody testing. A further group of children may lack pathognomonic features and a specific diagnosis may be made when an autoantibody is identified. A further group present with clinical features highly suggestive of an autoimmune encephalitis in whom an antibody is not identified.

Until recently for children no diagnostic criteria for autoimmune encephalitis had been established. Clinical studies have relied on expert opinion to classify aetiology in the absence of proven auto-antibodies.[5] Children with autoimmune encephalitis are typically polysymptomatic, with seizure, behavioural change, confusion and neuropsychiatric symptoms most frequently reported.[6]

In adults diagnostic criteria for autoimmune encephalitis have previously relied on the presence of antibodies, and response to immunotherapy.[7] Limitations of this approach are that this information is rarely available at presentation.

A broader diagnostic criteria for 'possible autoimmune encephalitis' was proposed by Graus et al. that required the presence of a) a subacute onset (rapid progression of less than 3 months) of working memory deficits, altered mental status or psychiatric symptoms AND b) at least one of: new focal CNS findings, seizures not explained by a previously known seizure disorder, CSF pleocytosis, MRI features suggestive of encephalitis AND c) reasonable exclusion of alternative causes.[8] These criteria differed from previously proposed criteria for a diagnosis of encephalitis[9] recognising that autoimmune encephalitis may occur without impaired consciousness, without fever, and with normal CSF and MRI findings. This approach applies a diagnostic framework which may encourage early consideration and treatment for possible autoimmune encephalitis without waiting for auto-antibody results.

More recently the diagnostic criteria proposed for adults[8] have been evaluated in children.[10] In a prospective cohort of 113 children identified from a multicentre study including children with definite (antibody confirmed) autoimmune encephalitis, a diagnosis of ADEM, and those with suspected autoimmune encephalitis. 103 of 113 fulfilled the criteria for possible autoimmune encephalitis. 46 of those children had no identifiable autoantibodies, with 21 receiving a final diagnosis of possible autoimmune encephalitis.[10]

A similar approach has been taken to clinically recognisable conditions. Criteria for diagnosis of probable anti-NMDA receptor encephalitis and Bickerstaff's encephalitis were similarly proposed.[8]

The proposed diagnostic criteria for probable anti-NMDA receptor encephalitis were subsequently evaluated in the paediatric population.[11] A diagnosis of probable anti-NMDA receptor encephalitis could be made when three proposed criteria were fulfilled:

a) rapid onset (< 3months) of at least four of the six following major groups of symptoms: 1) abnormal (psychiatric) behaviour or cognitive dysfunction; 2) speech dysfunction (pressured speech, verbal reduction, mutism); 3) seizures; 4) movement disorders, dyskinesias, or rigidity/abnormal postures; 5) decreased level of consciousness; and 6) autonomic dysfunction or central hypoventilation.

b) At least one of the following laboratory study results: 1) abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush or 2) CSF with pleocytosis or oligoclonal bands.

c) Reasonable exclusion of other disorders.[8]

A cohort of 29 paediatric patients with antibody confirmed anti-NMDA receptor encephalitis and 74 children with other encephalitis underwent review of case notes. During hospital admission 26 of 29 children with anti-NMDA receptor encephalitis fulfilled the Graus criteria, while only 3 of the 74 children with encephalitis of other aetiology. These criteria were both sensitive (90% sensitivity) and specific (96%). Although this validated the use of the proposed diagnostic criteria in children, the authors noted that not fulfilling the criteria did not exclude a diagnosis of anti-NMDA receptor encephalitis. The criteria were fulfilled during a prolonged admission, with only 24% of children fulfilling the criteria one week after of onset of symptoms, rising to 48% after two weeks of symptoms. This emphasises the importance of recognising probable NMDARE prior to the availability of antibodies and initiating early treatment.

Antibody testing

The 'ideal' auto-antibody would bind a protein expressed on the cell surface within the CNS. The presence of the antibody would be strongly associated with a clinical phenotype, and absent in the healthy population. In animal studies in which the antibody is introduced a similar clinical phenotype would develop, and would reflect the effect of interfering with the function of the cell surface protein on a genetic level.

In many conditions the above ideal conditions are not met and the pathogenic role of autoantibodies is not always clear. Many paraneoplastic conditions in adults are diagnosed by the presence of antibodies (Anti-Hu, Ma1/2, CV2) that have a strong association with a clinical phenotype but are not in themselves pathogenic. They are however useful disease biomarkers for other hitherto undetected pathogenic antibodies.

Hashimoto's encephalitis is a presumed autoimmune condition in which encephalopathy is associated with the presence of a subclinical or mild thyroid disorder and antibodies to thyroid peroxidase (TPO). The high prevalence of thyroid disorders, the presence of TPO antibodies in 13% of the healthy population,[12] and no in-vitro or in-vivo evidence of TPO antibodies inducing encephalitis in animal studies has caused ongoing debate regarding the validity of this diagnosis.[13]

A number of challenges have been faced in the development of assays to autoantibodies. Linear assays of MOG were found to be a non-specific marker of brain inflammation in the adult population,[14] until a cell-based assay and a restriction to IgG1 antibodies was employed. The use of live or fixed eukaryotic cells to express the full length antigen at the cell surface in its native conformation ensured only clinically relevant auto-reactivity was detected, and the assay became highly specific.[15]

Voltage gated potassium channel complex antibodies were detected in a wide range of conditions. The radioimmunoassay employed precipitated antibodies to a number of associated antigens including Leucine-rich, glioma inactivated 1 (LGI-1) and Contactin associated Protein 2 (CASPR2) and a number of other antigens.[16] Antibodies to LGI-1 and CASPR2 are associated with clinically distinct phenotypes in adult autoimmune encephalitis, while other antibodies to the VGKC complex were not associated with disease.

A number of antibodies have been identified which fulfil some if not all of the above conditions, and are associated with a recognisable clinical syndrome. These antibodies and associated clinical syndromes are considered individually below. It remains uncertain whether antibody testing of serum or CSF is preferable in each case, and the evidence for both is considered within each syndrome.

Imaging

Most children presenting with encephalopathy will undergo MRI scan of the brain. In many cases this may be normal, or demonstrate non-specific changes. In some parenchymal or white matter inflammation maybe detected and those characteristic to a particular syndrome are discussed below.

Autoimmune encephalitis syndromes

Developments in NMDA receptor encephalitis

Anti-NMDA receptor encephalitis (NMDARE) is the commonest and perhaps most well defined autoimmune encephalitis in children. In a retrospective review of children with encephalitis NMDARE was more common than any single infective aetiology.[17] NMDARE may affect adults and children, with approximately 1/3 of cases occurring under 18 years

of age, and 95% under the age of 45.[8] Initially described in young women, there is a strong female preponderance, which is absent in those under 12 years of age. Clinical features are varied. In a retrospective multicentre study of 577 patients with NMDARE, abnormal behaviour and cognition were the commonest initial presentations in children, followed by seizures and movement disorder.[18] Seizures were more common in younger children as a first presentation, but a similar constellation of symptoms was seen in all age groups by four weeks into the illness. Of 577 patients with NMARE, only 1% were mono-symptomatic, suggesting that patients presenting with abnormal behaviour in isolation are unlikely to have NMDARE.[18]

NMDARE carries a significant mortality, with 9.5% of patients dying during hospital admission.[18] With early recognition and treatment significant recovery has been reported in up to 85% of children with NMDARE[18] based on a basic assessment of disability: the modified Rankin scale. Recently follow-up studies in children using more sophisticated neurocognitive assessments have suggested residual difficulties in a much greater proportion. In a small follow-up study at a median of 31 months after illness 8/11 children had residual deficits indicating frontal lobe dysfunction.[19] In a cross-sectional study of 21 children who had received a diagnosis of NMDARE were assessed at a median 31 months after onset of symptoms. Sixteen underwent comprehensive neuropsychological assessment demonstrating lower sustained attention scores, poorer long and short term verbal memory, reaction time and visual memory, more fatigue and lower quality of life. While fatigue correlated with lower quality of life scores, neither correlated with difficulties in sustained attention or long term verbal memory.[20] In detailed interviews parents reported difficulties with word finding (24%), attention and concentration (18%), impulsivity (18%), anxiety (18%) and indecisiveness (12%).[20] A comparative study evaluating the impact of NMDARE on children and adults using the adaptive behaviour assessment system (ABAS-3) showed greater residual deficits in children compared to adult patients.[21]

Evidence for a greater neuropsychological burden on these children would support early engagement with neuropsychological counselling and support during rehabilitation.

New antibody associated syndromes

Myelin Oligodendrocyte associated Glycoprotein

Acute disseminated encephalomyelitis (ADEM) is an inflammatory condition of the central nervous system more commonly seen in children and young adults. Clinical presentation is heterogeneous, and is frequently preceded by a prodromal illness or immunisation.

The clinical history of ADEM is strongly suggestive of an autoimmune process, but it is only in the last 10 years that an antibody has been identified.

Myelin Oligodendrocyte glycoprotein (MOG) is expressed in the outermost lamellae of the developing myelin sheath. Anti-MOG antibodies (MOG-Ab) have been used in an animal model of demyelination for many years, and MOG-Ab has been evaluated as a potential auto-antibody in the pathogenesis of multiple sclerosis in adults, however in the

adult population early studies demonstrated poor specificity, with MOG-Ab detected in a variety of brain diseases.[22,23] These early studies utilised non-conformational assays. When MOG-Ab was tested using a cell based assay, assessing for antibodies to the exposed portion of the protein in its native state were test it was found to be highly specific to demyelinating disease, and present in up to 50% of children with ADEM.[24–26] MOG-Ab are also associated with optic neuritis, transverse myelitis, and neuromyelitis spectrum disorder (NMOSD).

ADEM is a heterogeneous condition both in presentation and outcome. While typically a monophasic condition a small proportion of children with ADEM will go on to have further episodes and develop multiphasic disseminated encephalomyelitis (MDEM). In a retrospective study the presence of MOG-Ab was a risk factor for subsequent relapse which was seen in 30% of MOG-Ab positive cases. Furthermore unlike antibody negative ADEM in which relapses were only seen within two years of initial event, relapse frequently occurred years after initial event.[27] The presence of MOG-Ab may therefore prove an important indicator of those children that may require closer follow-up and potentially long term immunomodulation.

MOG-Ab has also been implicated in the development of seizures both in the context of an ADEM presentation but also in the development of subsequent 'post-ADEM epilepsy'.[27] Oligoclonal bands were more frequently seen in those children that went on to develop post-ADEM epilepsy suggesting that ongoing inflammation may contribute to epileptogenesis manifesting in a true autoimmune epilepsy. More recently, in the study from Armangue and colleagues, 7% of children (22/296) with definite or possible encephalitis were identified to be MOG-Ab positive.[28]

The outcome has generally been deemed favourable, yet as in NMDARE at follow-up 43% of children showed impairment in specific cognitive or behavioural domains.[29] Whether the presence of MOG-Ab predicts a poorer neurocognitive outcome is unknown.

Glial Fibrillary Astrocytic Protein (GFAP) astrocytopathy

Meningoencephalitis is a relatively common acute neurological condition. In 2016 a case series of adult patients were described with a clinical picture of an autoimmune meningoencephalomyelitis associated with an astrocytic pattern of patient IgG binding on mouse tissue, with subsequent confirmation of IgG antibody binding to a cell based assay transfected with GFAPα.[30] These findings were confirmed in a retrospective cohort of patients in whom GFAPα-IgG was detected in serum or CSF.[31] 66 of 68 patients with GFAPα-IgG detected in the CSF presented with a meningoencephalomyelitic picture with headache and neck stiffness in 63%, and sore throat, fever, rhinorrhoea or cough in 39%. Ataxia was present in 38% and autonomic dysfunction in 23%. Inflammatory CSF was present in 92% of cases.

Ten of the 90 cases presented were children with median age 10 yrs (range 3-15 years). Seven presented with meningoencephalomyelitis. Ataxia and autonomic dysfunction were seen in 4/10, brainstem dysfunction in 2/10 and epilepsy in 1/10. Anti-NMDA receptor antibodies were detected in CSF in two of the ten children. All seven of the ten children who received immunotherapy demonstrated a favourable response.

As yet it is unclear what proportion of children with a meningoencephalitic presentation in whom an infective organism is not identified could have antibodies to GFAP, but this could potentially reflect an effective target for treatment.

Other antibodies

A number of different auto-antibodies have been implicated in the pathogenesis of autoimmune encephalitis, yet nearly half of possible autoimmune encephalitis cases will not have an autoantibody identified.[5,10]

A number of antibodies implicated in autoimmune encephalitis in adults have been reported in children. These include both neuronal surface antibodies, and antibodies to intracellular antigens, and have been extensively described in previous reviews.[6,10,32]

Measurement of disease

Measurement of disease severity may guide treatment decisions at presentation, assist in prognostication and contribute to the assessment of response to treatment. The modified Rankin Score (mRS) is a simple scoring system to quantify level of disability according to a 6 point scale, and has been widely used as an outcome measure in stroke. In paediatric NMDARE this scale showed significant improvement in 85% of children in whom treatment was instigated promptly.[33] The mRS lacks the sensitivity to detect more subtle neurocognitive morbidity that has been identified using more targeted scoring systems such as the Adaptive behaviour assessment system (ABAS-3)[21] and CANTAB neurocognitive batteries.[20]

A scoring system for autoimmune encephalitis comprising 9 domains (seizure, memory dysfunction, psychiatric symptoms, consciousness, language problems, dyskinesia/dystonia, gait instability and ataxia, brainstem dysfunction, and weakness) has been proposed and evaluated in adult patients with good interobserver reliability, and strong correlation with mRS and an arbitrary clinical impression of severity.[34] The clinical assessment scale in autoimmune encephalitis (CASE) score has shown promise as a metric of clinical course allowing quantification of response to treatment. A similar scoring system with 10 domains is being developed as the Childhood Autoimmune Encephalitis Scoring Tool (personal communication: Dale R and Thomas T).

Scoring systems have been developed in adults with NMDARE to aid in prognostication. The NMDAR encephalitis one-year functional status (NEOS) score was developed by evaluating predictors of the mRS at one year after onset of disease.[35] Admission to intensive care, delay of treatment of more than four weeks from onset of symptoms, lack of clinical recovery within four weeks, abnormal MRI and CSF white cell count >20 cells/microlitre each contribute a point to create a score out of 5. A poor functional outcome (mRS $\geq$ 3) was seen in 3% of patients with a NEOS score of 0 or 1, and 69% of patients with a NEOS score of 4 or 5.[35]

Treatment and management of autoimmune encephalitides

While there are limited data to inform the choice of treatment for autoimmune encephalitis, a systematic review of the treatments of adult and children with autoimmune encephalitis found evidence to support three themes: 1) patients given immunotherapy do better and relapse less than patients given no treatment; 2) patients given early treatment do better and 3) when patients fail first line therapy, second line therapy improves outcome and reduces relapses.[36] Despite the paucity of randomised controlled studies to guide treatment, a general approach has been established while therapeutic preferences may vary between centres.

First line treatment

Where a trigger is identified, either infective or neoplastic then this should be addressed early. First line treatment almost invariably includes corticosteroids, with the benefit of a broad mechanisms of immune modulation, modulation of the blood-brain barrier and effective penetration of the central nervous system.[37]

In addition to corticosteroids both Intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) are commonly used. There is low grade evidence for IVIG improving outcome in NMDARE in children,[38] while a systematic review of the use of plasma exchange in conjunction with corticosteroids may improve outcome in NMDARE.[39] There are no data to inform a benefit of PLEX over IVIG therefore this is often guided by local preference and availability, and the challenges inherent in delivering PLEX to an agitated child.

Second line treatment

While many children with autoimmune encephalitis will respond to these first line treatments within one to two weeks a proportion will require second line therapy. In the treatment of NMDARE and other antibody mediated syndromes this is commonly Rituximab. Rituximab will deplete B-cells, but does not target plasma cells directly, and has a broad immune suppressant action modulating T-cell responses.[4] While generally well tolerated, in a retrospective review of 144 children receiving Rituximab for autoimmune or inflammatory CNS disease infusion reactions were reported in 12% of children.[40] Four patients (3%) suffered a serious infectious adverse event with two fatalities (1.4%).

Monitoring of B-cell levels at 2-4 weeks has been recommended to ensure adequate depletion, with periodic monitoring to assess for repopulation, alongside immunoglobulins to monitor for hypogammaglobulinaemia.[4]

Co-treatment with cyclophosphamide is commonly used in adult patients with NMDARE, providing broad immune suppressive effects. Cyclophosphamide may be indicated in children who have failed to respond to Rituximab. In a retrospective review of paediatric patients with autoimmune and inflammatory CNS disease children who received dual therapy with Rituximab and Cyclophosphamide suffered no greater side effects than those on Rituximab alone.[40]

Third line treatment

A proportion of patients may be refractory to both first and second line treatments and there is emerging evidence for treatment with third line agents.

Tocilizumab, an inhibitor of the inflammatory cytokine Interleukin-6 which is key to the differentiation and survival of plasma cells, has been used in the treatment of refractory autoimmune encephalitis in adults,[41] with reports of successful use in children.[42] Similarly, plasma cells are targeted by the proteasome inhibitor Bortezomib, which has been used in the treatment of refractory NMDARE in adults.

Interleukin 2 has been used at a low dose which preferentially activates T regulatory cells in the treatment of refractory autoimmune encephalitis with no reported side effects and some efficacy.[43]

While these broad treatment strategies are employed for autoimmune encephalitis irrespective of antibody status, the differing syndromes may have a different clinical course and response to treatment. MOG associated disease is reported to be largely responsive to first line treatment less commonly requiring escalation of acute treatment.

While the relapse rate for autoimmune encephalitis is reported to be low, it varies between conditions. A relapse rate of 12% within two years has been reported for adults with NMDARE,[18] while relapse rates for children with MOG associated demyelination have been reported between 30-50%.[27,44] For children with relapsing NMDARE a chronic immune suppression strategy may be considered of continued Rituximab, mycophenolate mofetil or azathioprine may be considered.[45] There are few studies to guide the treatment of relapsing MOG disease but approaches have included low dose steroids, monthly IVIG, and mycophenolate mofetil.

Challenges ahead

Establishing diagnostic criteria for autoimmune encephalitis that can be applied using information available at presentation and have been validated in children will be crucial in establishing standardisation of therapy, and robust therapeutic trials. While a broad approach to treatment of presumed autoimmune encephalitis is shared by most centres, there is little data to support current practice. Results of clinical trials such as the IgNITe trial, a randomised placebo controlled trial evaluating the use of IVIG in the management of paediatric encephalitis are eagerly awaited.

Antibody testing has become widely available in the past five years, with an increasing repertoire of tests and reducing costs. As turn around time for tests improves this may allow antibody status to dictate initial management, but in most centres this is some way off. As antibody testing becomes more widespread, it is likely that previously heterogeneous conditions such as ADEM may be further classified by antibody status and a stronger phenotype may be seen. Conversely, increased antibody testing may see a wider phenotype of disease associated with particular antibodies, as has been seen in Glycine receptor antibodies in children. The challenge will continue to be interpreting the significance of positive antibody results beyond the described presentation.

Research continues to develop our understanding of subtypes of autoimmune encephalitis There is increasing appreciation of the long term neurocognitive morbidity associated with NMDARE. A deeper understanding of the functional impact of the autoimmunity will help prognosticate, and may direct treatment timing and modality.

The association of MOG-Ab with a large proportion of ADEM cases may allow more accurate prognostication at first presentation. As our understanding of the natural history of MOG associated disease in children develops, antibody testing may start to dictate decisions regarding on-going immunomodulation.

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Autoimmune Epilepsy – A Growing Etiological Class in Epileptology

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Introduction

Autoimmunity as a major pathogenic mechanism of epilepsy has become a hot topic in epileptology. Immune etiology has been listed as one of the five etiologies of epilepsy in the latest ILAE epilepsy classification[1]. It embraces epilepsy directly resulted from immune disorders in which seizure is a core symptom. Various types of autoimmune epilepsy generally have typical clinical, imaging, serological and cerebrospinal fluid (CSF) characteristics. Encephalitis associated with specific anti-neuronal autoantibodies are typical examples of autoimmune epilepsy. Also, other autoimmune central nervous system (CNS) disorders, such as demyelinating diseases, could present with seizure as a major symptom. Besides, certain systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), could result in seizures when the CNS is involved. In an even broader sense, epilepsy in a patient may be presumed to have an immune cause even without positivity of autoimmune antibodies if the clinical context is compatible and other causes have been reasonably excluded. As the repertoire of autoantibodies grows, autoimmune causes may gain a greater share in the etiologies of epilepsy. In this paper, we would try to review the categories of autoimmune epilepsy disorders and describe how autoimmunity as a cause implicates the management of epilepsy. In this review, we will use autoimmune epilepsy interchangeably with immune epilepsy as proposed by the ILAE.

Autoimmune encephalitis with positive antineuronal autoantibodies

Autoimmune encephalitis has raised widespread attention since the discovery of Anti-NMDA receptor autoantibody by Dalmau group in 2007[2]. A tremendous amount of basic science and clinical researches have been focused on this topic. Epilepsy is a core feature of these encephalitic syndromes, either at initial presentation or as one of the sequelae of these encephalitic syndromes. The autoantibodies can be grouped according to their targeted molecules, present either on the neuronal membrane surface or intracellularly (Table)[3]. For autoantibodies targeting surface antigens, they probably disrupt synaptic function and plasticity.

Autoantibodies targeting the intracellular neuronal antigens could initiate immune attack of the CNS. The mechanism of production of these autoantibodies is mostly elusive. Molecular mimicry has been proposed, as some of the autoimmune encephalitis are paraneoplastic in nature. Associated tumors may contain neuronal tissue or express neuronal proteins[4].

	Syndrome	Diagnostic assay	Frequency of Cancer	Main Type of Cancer
Antibodies against intracellular antigens				
Hu (ANNA1)	Limbic encephalitis	Western blot	>95%	Small-cell lung carcinoma
Ma2	Limbic encephalitis	Western blot	>95%	Testicular seminoma
GAD	Limbic encephalitis	Radioimmunoassay	25%	Thymoma, small-cell lung carcinoma
Antibodies against synaptic receptors				
NMDA receptor	Anti-NMDA receptor encephalitis	Cell-based assay	Varies with age and sex	Ovarian teratoma
AMPA receptor	Limbic encephalitis	Cell-based assay	65%	Thymoma, small-cell lung carcinoma
$GABA_B$ receptor	Limbic encephalitis	Cell-based assay	50%	Small-cell lung carcinoma
$GABA_A$ receptor	Encephalitis	Cell-based assay	<5%	Thymoma
mGluR5	Encephalitis	Cell-based assay	70%	Hodgkin's lymphoma
Dopamine receptor	Basal ganglia encephalitis	Cell-based assay	0%	-
Antibodies against ion channels and other cell-surface proteins				
LGI1	Limbic encephalitis	Cell-based assay	5-10%	Thymoma
CASPR2	Morvan's syndrome or limbic encephalitis	Cell-based assay	20-50%	Thymoma
DPPX	Encephalitis	Cell-based assay	<10%	Lymphoma
MOG	Acute disseminated encephalomyelitis	Cell-based assay	0%	-
Aquaporin 4	Encephalitis	Cell-based assay	0%	-
GQ1b	Bickerstaff's brainstem encephalitis	ELISA	0%	-

Table: Antibodies in the diagnosis of autoimmune encephalitis [37]. AMPA=alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA= antineuronal nuclear antibody; CASPR2=contactin associated protein; DPPX=dipeptidyl-peptidase-like protein-6; ELISA= enzyme-linked immunosorbent assay; GABA=gamma-Aminobutyric acid; GAD=glutamic acid decarboxylase; GQ1b= Ganglioside Q1b; LGI1=leucine-rich glioma inactivated; mGluR=metabotropic glutamate receptor; MOG=myelin oligodendrocyte glycoprotein; NMDA= N-methyl-D-aspartate.

Various types of autoimmune encephalitis have specific clinical presentations which provide diagnostic clues, though overlap is common. The clinical presentation depends on the part of the neuronal system targeted by the autoantibody. Anti-NMDA receptor encephalitis is a well-described entity which is a typical example for illustration.

Anti-NMDA Receptor Encephalitis

Anti-NMDA receptor encephalitis can be regarded as a paraneoplastic syndrome. It is associated with ovarian teratoma. Other tumors have also been reported[5]. However, it is notable that tumor is absent in a significant portion of cases, especially in the pediatric age group[6].

Anti-NMDA receptor encephalitis is characterized by prominent neuropsychiatric features such as hallucinations, behavioral changes and agitation, in association with neurological alterations such as decrease in conscious level and autonomic instability[7, 8]. Seizure is common during the course of disease, and is one of six major diagnostic criteria for the condition[9, 10]. It can occur early before other neuropsychiatric manifestations in children[11]. Extreme delta brush is pathognomonic for the condition, although focal or diffuse slowing, epileptiform discharge or disorganized activity may also occur[12, 13]. It is a complex with delta slow waves, with 20-30Hz beta activities riding on the delta waves.

The anti-NMDA receptor antibody is itself pathogenic[14, 15]. It binds to NMDA receptors which are concentrated over forebrain and limbic system, most notably the hippocampus[16]. This may explain the typical MRI brain findings of limbic encephalitis with abnormal T2W hyperintensities over the bilateral mesial temporal regions. Binding of the anti-NMDA receptor antibody to NMDA receptor results in internalization of the NMDA receptor. This in turn decreases the NMDA receptor density on neuronal surface and attenuates the currents of ion entry through the membrane channel[14].

It has been proposed that molecular mimicry plays an important role in the pathogenesis of anti-NMDA receptor encephalitis. Expression of NMDA receptor in teratomas may induce production of anti-NMDA autoantibodies by plasma cells[17]. The autoantibodies could then cross-react with NMDA receptors in the CNS after crossing the blood brain barrier, resulting in limbic encephalitis. Molecular mimicry may not only occur in neoplasms. Novel development of anti-NMDA receptor autoantibodies can occur after herpes simplex encephalitis (HSE)[18]. Anti-NMDA receptor antibodies could be detected in up to 30% in HSE patients and some of them do manifest as anti-NMDA receptor encephalitis. In children, this post-HSE anti-NMDA syndrome predominantly manifests as choreoathetosis, while psychiatric presentations are commonly seen in adults[18, 19]. Although the exact pathogenic mechanism is still uncertain, HSE probably triggers plasma cells to produce anti-NMDA receptor autoantibodies.

Other Autoantibody-Mediated Encephalitis or CNS paraneoplastic syndromes

After the discovery of anti-NMDA receptor encephalitis, more and more autoimmune encephalitis with specific autoantibodies have been reported in recent years. Anti-VGKC, including the anti-LGI1 and anti-CASPR2, and anti-GABA receptors are examples of autoantibodies aiming at neuronal surface target antigens. Anti-Hu and anti-Yo are examples of autoantibodies targeting intracellular antigens. Seizures are common in these autoimmune syndromes. Anti-LGI1 is associated with a specific form of seizure, known as faciobrachial dystonic seizure. This is a brief dystonic contraction of the upper limb and facial muscles involving one side of the body. It usually lasts for seconds only. It could be mistaken as myoclonus or dystonia[20]. EEG could demonstrate ictal focal epileptiform discharges over the frontotemporal regions. Clinical syndromes associated with autoantibodies against surface or

synaptic antigens tend to be more responsive to immunotherapy. Syndromes associated with autoantibodies targeting intracellular antigens are less amenable to immunotherapy and less common in children[3].

Autoimmune CNS diseases associated with Epilepsy

Demyelinating diseases of the CNS can also manifest as seizure. The spectrum ranges from monophasic diseases such as acute disseminated encephalomyelitis (ADEM) to relapsing diseases such as multiple sclerosis (MS), myelin oligodendrocyte glycoprotein encephalomyelitis (MOG-EM) and neuromyelitis optica (NMO). Specific autoantibodies could be found in certain syndromes such as anti-MOG in MOG-EM and anti-aquaporin-4 in NMO. In other demyelinating syndromes, such as MS, the culprit autoantibodies remain elusive. Epilepsy is about 3 times more common in MS when compared with the general population[21]. Seizures, mostly focal in onset, occur in up to about 20% of MOG-EM patients and are much more common than in NMO spectrum disorders[22]. Cortical and subcortical lesions are commonly seen in these epileptic patients. Chronic epilepsy could be a complication in up to 16% of children with monophasic ADEM[23]. Presence of anti-MOG autoantibodies may help to predict the epilepsy sequelae.

Rasmussen encephalitis (RE) is a rare neurological disorder. It affects mainly the pediatric group with onset ranging from infancy to early adulthood with median age of six years old[24]. It is a chronic focal encephalitis characterized by uncontrolled focal seizures, progressive unilateral hemispheric cerebral atrophy resulting in focal neurological deficits. The course of disease can be divided into three stages: the prodromal, acute and residual stages. Prodromal stage involves relative less frequent seizures and mild hemiplegia. Acute stage has prominent seizures. Epilepsia partialis continua (EPC) is the typical seizure type in this stage. Residual stage is the final phase which is characterized by static permanent hemiplegia and chronic epilepsy. EEG features evolve through various stages of the disease[25]. Focal slow waves would develop over the atrophic side of cerebral hemisphere in the early stages. Interictal epileptiform discharges and features of EPC would then emerge. In more than half of the cases, interictal activities would later spread to the unaffected hemisphere. MRI imaging showed progressive hemispheric atrophy initiated from perisylvian region. PET and SPECT classically show hypometabolism over the affected cerebral hemisphere.

RE is probably immune in nature. Autoantibodies, including anti-GluR3, has been proposed to be important in pathogenesis. However, only a minor proportion of patients have been detected to be autoantibody positive. Plasmapheresis has failed to show consistent benefit in RE. Cytotoxic T-cells have been demonstrated to be active in attacking neurons and astrocytes in RE[26]. Microglial cells can induce seizures and neurodegeneration through releasing pro-inflammatory cytokines such as IL-1 and inducing complement-mediated synaptic stripping to increase network excitability[27, 28]. All these suggest autoimmunity plays a central role in RE pathogenesis. Research has yet to be done to identify the exact autoimmune target that initiates the subsequent destructive inflammatory response.

Seizure may also occur in other systemic autoimmune diseases. In SLE, seizure is relatively common, occurring in 5% to 50% of the cases[29]. Seizure is part of the American College of Rheumatology's criteria for neuropsychiatric lupus[30]. Hashimoto's encephalitis (HE), which is now commonly known as steroid responsive encephalitis, is associated

with anti-thyroid antibodies. Seizures, movement disorders and psychiatric symptoms are common features. Patients are commonly euthyroid or just mildly hypothyroid in HE. Hence, the development of encephalitis is likely to be independent of thyroid function[31]. Pathogenesis of this autoimmune encephalitis is still not well understood. Cerebral vasculitis model has been proposed based on several cases with histopathological study. The pathogenic role of the autoantibodies is obscure. Intrathecal synthesis of the autoantibodies has been postulated to be the key mechanism in the pathogenesis of HE[32]. There is some evidence that the autoantibodies are directly antineuronal. The antigenic targets are suspected to be cortical neurons for anti-TSH-R IgG and cerebral vasculature for anti-TG IgG[33]. However, the specificity of the autoantibodies is questionable as it could also be found in other autoimmune diseases or even in the normal population.

FIRES and NORSE

FIRES is a clinical syndrome in which a child or adolescent without prior epilepsy presents with status epilepticus following a non-specific febrile illness which is prolonged and often refractory or super-refractory. Its counterpart in adults is referred as NORSE. The prognosis is poor with high mortality expected in the acute phase[34]. Subsequent refractory epilepsy with disabling cognitive decline is common among survivors[35]. Whilst the exact etiology of FIRES and NORSE remains uncertain, autoimmunity has been postulated to be the likely mechanism. Early initiation of immunotherapy and monitoring clinical signs while waiting for the autoantibody results are a common practice in cases of FIRES and NORSE. Other treatment options such has hypothermia and ketogenic diet has also been proposed.

Work up for a suspected case of autoimmune epilepsy

When a person develops his/her first-ever seizure that evolves into prolonged or refractory status epilepticus, or refractory seizures in association with neuropsychiatric symptoms, autoimmune etiology should be seriously considered. Standard investigations must be done to look for infective, metabolic or structural causes of the new-onset seizure. These essentially include microbiological workup such as CSF examination, blood tests to look for uremia, electrolyte or metabolic disturbances and neuroimaging to look for structural lesions such as neoplasm or encephalitis. Once these etiologies have been reasonably excluded, the clinical question is further workup plus or minus empirical treatment of presumed immune cause of epilepsy. Serum or CSF could be sent for autoimmune antibody testing. However, not all the clinical units have the privilege to have a complete autoantibody panel at hand. In our institute, a limited antibody panel is available, and we often need to send serum or CSF samples overseas for extended testing which is expensive and requires a relatively long turnaround time. On the other hand, negative tests do not entirely exclude autoimmune causes[36]. False negatives could be due to immunotherapy or chemotherapy that the patient is receiving. Criteria have been published for early diagnosis and empirical treatment of the autoimmune encephalitis[37]. A clinical presentation of subacute seizures, neuropsychiatric symptoms pointing to limbic system dysfunction, CSF pleocytosis, mesial temporal T2W hyperintensities in MRI and EEG with epileptiform discharges over temporal lobes is suggestive of autoimmune encephalitis.

As many of the autoimmune encephalitis may herald a paraneoplastic phenomenon, investigations for tumor screening should be initiated[38]. Depending on the likelihood of an underlying tumour, the workup may include specific imaging of various body regions such as mammogram, CT of the thoracic, abdominal or pelvic regions, or even PET-CT of the whole body which may be more sensitive.

Treatment of epilepsy due to autoimmune causes

Apart from use of anti-epileptic drugs, treatment should be targeted towards the underlying autoimmunity. The first line treatment is mainly high dose steroid, IVIg, PLEX (plasmapheresis) or a combination of the three. Rituximab and cyclophosphamide are generally regarded as second line therapies if response to the first line is suboptimal. There has been a recent trend to introduce rituximab earlier due to its reliable safety profile, though this remains a self-financed item under this indication within the Hospital Authority[6, 39].

Different subtypes of autoimmune encephalitis could have different responses to different immunotherapy modalities. As mentioned above, autoantibody tests may not be readily available and the results can take a long time to be released, empirical treatment is often given in suspected cases after other causes have been preliminarily ruled out. However, such tests are important not only for diagnosis but also for prognosis and formulation of a treatment plan. For autoantibody positive cases, there has not been a consensus on whether maintenance treatment is indicated and how it should be given[6, 39]. However, treatment should be guided by the expected likelihood of relapse and the potential disability caused by such occurrences. The treatment of autoantibody negative cases is even more complicated. It is still uncertain whether immunotherapy should be maintained lifelong if the patient is treatment responsive, or to what extent immunotherapy should be escalated in case first-line treatment results in suboptimal response.

Epilepsy surgery is still the mainstay of treatment for RE[24]. Complete disconnection of the affected hemisphere either by hemispherectomy or hemispherotomy is the common approach. The timing of the surgery has to balance both control of the disease and preservation of neurological function. In other autoantibody-positive autoimmune encephalitis, outcomes of epilepsy surgery seem to be less favorable than other causes of refractory epilepsy[40, 41]. However, these comments were made based on small cohort studies only. More data from larger studies is needed.

Conclusion

Autoimmune epilepsy is an important etiological group of epilepsy. Its importance is growing as more autoantibodies are discovered. Many of the entities in this group have a good response to immunotherapies. The best regimens of treatment at both acute and long-term phases have yet to be determined by future research.

List of Abbreviations

CASPR 2	Contactin-associated protein 2
EEG	Electroencephalography
FIRES	Febrile infection-related epilepsy syndrome
IG	Immunoglobulin
IL	Interleukin
LGI1	Leucine-rich glioma inactivated 1
MRI	Magnetic Resonance Imaging
NMDA	N-methyl-D-aspartate
NORSE	New-onset refractory status epilepticus
PET	Positron emission tomography
SLE	Systemic Lupus Erythematosus
SPECT	Single Photon Emission Computed Tomography
TG	Thyroglobulin
TSH-R	Thyroid-stimulating hormone receptor
VGKC	Voltage gated potassium channel-complex

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Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease in children

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Introduction

'Acquired demyelinating syndromes (ADS)' is an umbrella term used to describe a spectrum of inflammatory demyelinating diseases of the central nervous system (CNS). The incidence of ADS ranges from 0.80-1.66 per 100,000 children[1-3]. Diagnostic criteria from the International Paediatric Multiple Sclerosis Study Group (IPMSSG) are available for different clinical subtypes of ADS, including acute disseminated encephalomyelitis (ADEM), clinically isolated syndrome (CIS), multiple sclerosis (MS) and neuromyelitis optica (NMO)[4]. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease is a relatively new type of antibody-mediated ADS. MOG is a glycoprotein comprising 245 amino acids that is expressed exclusively on the surface of myelin sheath and oligodendrocytes, which are glial cells of the CNS, and is assessable by a humoral immune reaction[5, 6]. Various paediatric studies revealed that up to one third of children with a first episode of ADS harbor serum MOG antibodies[7, 8]. MOG antibody-associated disease has various clinical presentations. It is important to differentiate MOG antibody-associated disease from other kinds of ADS, e.g. multiple sclerosis or aquaporin-4 (AQP-4) antibody-associated disease, as management and outcome are different. Particularly, MOG antibody-associated disease is distinct from multiple sclerosis and the presence of MOG antibody indicates a non-multiple sclerosis disease course[7, 8]. MOG antibody-associated disease is now considered a new disease entity. This review describes the clinical presentation, treatment and prognosis of MOG antibody-associated disease, with emphasis on children.

Clinical presentation

The clinical spectrum of MOG antibody-associated disease is broad, which includes ADEM, optic neuritis (ON), transverse myelitis (TM), neuromyelitis optica spectrum disorder (NMOSD), brainstem syndromes and focal cortical diseases. It can be monophasic or relapsing, but not progressive. It can present in any age group, sex or ethnicity[9].

Acute disseminated encephalomyelitis (ADEM)

ADEM is an acute inflammatory demyelinating condition of the CNS, which presents clinically as new onset encephalopathy and polyfocal neurological features. It is a typical onset presentation of MOG antibody-associated disease in children, particularly in young children. According to a UK study, 36% of patients younger than 20 years presented with ADEM[9]. The Austria group revealed that 58% of children with ADEM as the first demyelinating event have MOG antibodies[10]. The same study demonstrated that children with MOG antibodies did not differ in their age at presentation, sex ratio, the presence of oligoclonal bands, clinical symptoms or initial severity, apart from a higher CSF cell count, compared with children without MOG antibodies[10]. However, children with MOG antibodies tend to have large, hazy, bilateral MRI lesions, and atypical MRI lesions (small, well defined lesions) were usually absent, when compared with children without MOG antibodies[10]. In

children younger than 7 years of age, MRI patterns of confluent, largely symmetrical lesions mimicking leucodystrophy may be seen[11].

Optic neuritis (ON)

Optic neuritis is the inflammation of optic nerves, characterized by visual loss. It is the most common type of onset attack considering all age groups[9]. It can be unilateral or bilateral. Bilateral involvement is more common in MOG antibody-associated ON or AQP4 antibody-associated ON, when compared with MS associated-ON (84% vs 82% vs 23%)[12]. The optic nerve involvement in MOG antibody-associated ON is typically anterior and presents with optic nerve head swelling. On the other hand, the posterior optic nerve and optic chiasm are typically involved in AQP4 antibody-associated ON[12]. Most cases (>80%) of MOG antibody-associated ON resolved without permanent visual disability (visual acuity 6/36 or worse in at least one eye)[9].

Transverse myelitis (TM)

Transverse myelitis associated with MOG antibody typically presents as longitudinally extensive transverse myelitis (LETM), which is defined on MR scan as extending continuously over at least three vertebral segments. It often affects the lower thoracic region and conus[13, 14]. The involvement of conus may explain the disproportionate sphincter and erectile dysfunction.

Neuromyelitis optica spectrum disorders (NMOSD)

NMO is a type of ADS associated with serum AQP-4 antibody. A new nomenclature, NMOSD, was introduced by the International Panel for NMO Diagnosis (IPND) in 2015. NMOSD was stratified by serologic testing, into NMOSD with or without AQP4 antibody[15]. Diagnostic criteria with core clinical (1. optic neuritis, 2. acute myelitis, 3. area postrema syndrome, 4. acute brainstem syndrome, 5. symptomatic narcolepsy or acute symptomatic diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, 6. symptomatic cerebral syndrome with NMOSD-typical brain lesions) and radiological characteristics are available for NMOSD in adults, which are also considered appropriate for paediatric patients[15]. More stringent criteria with additional MRI features are required for diagnosis of NMOSD without AQP-4 antibody[15]. The diagnostic criteria allow incorporation of cases of NMOSD associated with other specific autoantibodies[15]. Various studies showed that MOG antibody could be detected in AQP4 antibody negative NMOSD patients, including children[9, 13, 14, 16, 17].

Cortical encephalitis

Cortical encephalitis is an unusual presentation. It presents with seizures, sometimes with abnormal behavior or focal symptoms. It is usually unilateral. MRI brain in the acute phase shows unilateral mildly oedematous cortical lesion(s) best seen on fluid-attenuated inversion recovery images. It was reported in both adult and paediatric age groups[18, 19].

Brainstem attacks

One study revealed that brainstem involvement was present in around one third of MOG antibody positive patients with ON and/or myelitis. Clinical manifestations are diverse

and may include symptoms typically seen in AQP4 antibody-associated NMO, such as intractable nausea and vomiting and respiratory insufficiency, or in multiple sclerosis, such as internuclear ophthalmoplegia. All reported cases were adult patients[20].

Diagnosis

MOG antibody-associated disease is now considered a condition distinct from multiple sclerosis and AQP4 antibody-associated NMOSD. Diagnostic criteria for MOG-associated disorders were proposed by different groups, based on clinical, laboratory with or without radiological or electrophysiological characteristics[21, 22].

Various clinical presentations of MOG antibody-associated disorders have been discussed in the above section. It is vital for clinicians to consider other possible congenital or acquired conditions, which may mimic ADS, as there are important therapeutic and prognostic implications.

Laboratory diagnosis is based on demonstration of the MOG antibody in serum by an optimized cell based assay using a full-length conformationally intact MOG construct and a secondary antibody binding to class 1 IgG[23]. As data suggested peripheral production of antibodies, analysis of serum samples results in higher specificity than CSF samples. Serum analysis is sufficient in most situations[24]. In order to avoid over testing of this rare biomarker and significantly reduce the positive predictive value of the test, experts have proposed indications for MOG antibody testing[22]. For instance, MOG antibody analysis is not recommended in typical MS.

Lumbar puncture may be performed in patients presenting with ADS, but CSF findings are not included in those two sets of proposed diagnostic criteria[21, 22]. According to a UK study, 38% of patients with MOG antibody-associated disease had an elevated CSF white cell count (>10/uL) and 46% of patients had an elevated CSF protein concentration (>0.5g/L)[9]. Intrathecal synthesis of oligoclonal band was present in 12% of patients[9]. Therefore, it is important to appreciate that normal CSF findings do not exclude the diagnosis of MOG antibody-associated disease.

Treatment

Acute attacks are usually treated with 3 to 7 days of high dose intravenous methylprednisolone followed by oral prednisolone. Plasmapheresis can be initiated for management of severe acute attacks or suboptimal response to steroid therapy[23]. The optimal duration of initial immunosuppression after the first attack was not very clear. However, evidence showed that the risk of relapse was higher in those who were not immunosuppressed or immunosuppressed for less than 3 months, when compared with those who were treated for longer than 3 months[9]. Therefore, some experts recommend low dose oral prednisolone or immunosuppressant for 6 months after the initial attack[23]. Steroid sparing agents such as azathioprine or mycophenolate mofetil can be considered if long-term steroid is needed[25, 26]. Rituximab has also been used as maintenance therapy[25, 26]. Multiple sclerosis disease modifying therapy, which may worsen AQP4 antibody-associated disease, is not recommended in patients with MOG antibody-associated disease[25, 27].

Prognosis

According to a UK study, which involved 252 patients, recovery from the onset attack was full or good in 78% of patients. Full recovery was more frequent in patients with unilateral optic neuritis and ADEM-like presentation. Younger patients (<20 years) were more likely to achieve full recovery when compared with older patients[9]. The same study showed that relapse risk was higher in those who were not immunosuppressed or immunosuppressed for shorter than 3 months, when compared with those treated for longer than 3 months[9]. Analysis of another smaller cohort from the same study illustrated that relapses tended to occur early or shortly after stopping steroids[9].

Studies showed that persistent MOG antibody positivity was significantly associated with a recurrent non-MS disease course[28, 29]. A study of adult and paediatric seropositive ADEM patients demonstrated that 88% of patients with persistent MOG antibodies relapsed during follow up, when compared to 12% with transient MOG antibodies[21]. Disappearance of MOG antibodies seems to indicate remission[9]. Serial testing of MOG antibody is therefore useful, especially before stopping immunosuppressive therapy.

Although MOG antibody-associated disease is generally considered to be less disabling than AQP4 antibody-associated NMOSD, some patients have residual disability[30]. Analysis of 75 patients (mean age at onset +/- SD = 29 +/- 16.5 years) revealed that permanent disability occurred in about half of the patients and more often involves sphincter and erectile dysfunction than vision and mobility. Transverse myelitis at onset was a significant predictor of long-term disability[9].

Conclusion

MOG antibody-associated disease is a new entity of acquired demyelinating syndrome. There are still many unanswered questions. Local study of MOG antibody-associated disease is lacking. In view of the low incidence, collaboration between paediatric and adult neurology colleagues is of utmost importance.

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Management of Optic Neuritis - from the Perspective of Neuro-ophthalmologists

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Optic neuritis is the inflammation of the optic nerve, which can lead to optic atrophy and irreversible visual loss in some cases, if not appropriately managed. It can be infective or non-infective in origin. Most cases of optic neuritis encountered in Hong Kong are non-infective or autoimmune in origin. Non-infectious optic neuritis can occur in isolation, in which case it is referred to as idiopathic optic neuritis, or in the context of (or as harbinger of) systemic conditions such as multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), acute disseminated encephalomyelitis (ADEM), etc. Distinct differences exist between the Caucasian and Asian populations in terms of epidemiology, clinical course and association with other neuro-inflammatory syndromes. Although young- to middle-aged adults are the most commonly affected, paediatric optic neuritis (PON) is a well-recognized entity that has different clinical characteristics from the adult variety. Despite the reported overall favourable outcomes of optic neuritis, careful attention to the exact etiology and individualized treatment is important to prevent irreversible visual loss and to detect any underlying systemic disease. The management of optic neuritis, in particular with reference to the local Chinese population and paediatric age group, is reviewed here.

Demographics

The annual incidence of acute optic neuritis has been estimated to be 1–5 per 100,000[1-8] In Olmstead County, Minnesota, United States, the incidence rate is estimated to be 5.1 per 100,000 person-years and the prevalence rate 115 per 100,000.[1] The rates vary across different geographical locations and ethnic groups, partly reflecting the distribution of MS.[9] In Asia, the annual incidence rate of optic neuritis in Japan and Taiwan were 1.6 per 100,000 person-years[10] and 0.3 per 1000 person-years[11] respectively.

Optic neuritis has female preponderance and affects young adults. In the ONTT, 77% of the patients were female with mean age was 32 ± 7 years.[12]

Although rare in comparison to the adult variety, optic neuritis can also affect children, with incidence of 0.2 per 100,000 person-years from a Canadian study.[13] The affected children are also more often female than male, but this preponderance is of lower magnitude than that for adults (2-3:1 female: male ratio vs 9:1 for adults).[14-16] The age cutoff for PON was not clearly defined, but it has been taken arbitrarily in most studies to be eighteen years of age.[17] It has been observed that younger children (pre-pubertal) tend to have a more "paediatric" form of optic neuritis than the older ones (post-pubertal), who have clinical features similar to those of the "adult" form (see below)[17, 18].

Classification of optic neuritis

There is limited consensus regarding the systematic nosology for optic neuritis.

Optic neuritis can be broadly classified into infectious and non-infectious. Infectious causes, amongst others, include syphilis[19] (especially if co-infected with human immunodeficiency virus)[20], tuberculosis[21], mumps[22], measles[23], etc. It can also be associated with paranasal sinusitis.[24-26]

In general, the term optic neuritis refers to the non-infectious type, which is more common. It can be further classified according to the magnetic resonance imaging (MRI) features, laboratory findings (e.g. oligoclonal band [OCB], aquaporin-4 [AQP4]-IgG, anti-myelin oligodendrocyte glycoprotein [MOG]-IgG, *etc*) and clinical features (isolated or with other neurological/systemic symptoms and signs).

Optic neuritis caused by a primary demyelinating process usually has favourable recovery from an attack with or without corticosteroid (i.e. steroid is optional). In the absence of any systemic clinical signs and symptoms, MRI abnormalities in addition to optic neuritis, and negative laboratory findings, it is termed idiopathic optic neuritis (monophasic or recurrent). If the MRI is abnormal, the diagnosis may be MS (if the 2017 revised McDonald criteria are met), ADEM or clinically isolated syndrome (CIS) depending on the MRI and clinical features.

On the other hand, for optic neuritis that is caused by a primary autoimmune process, the response to corticosteroid treatment is generally remarkable (i.e. steroid-responsive). It can be isolated, as in the case of chronic relapsing inflammatory optic neuropathy (CRION) or MOG-IgG-related optic neuritis. It can also be associated with systemic condition such as NMOSD and other autoimmune disorders (e.g. systemic lupus erythematosus (SLE) or sarcoidosis).

Neuroretinitis and optic perineuritis are not strictly classified as optic neuritis but they have overlapping clinical features with optic neuritis.

On clinical ground, optic neuritis can be classified as typical and atypical. 'Typical' optic neuritis runs the clinical course of a demyelinating disease, implying its association with MS/CIS, whereas 'atypical' optic neuritis is more likely to be associated with other conditions, such as NMOSD, systemic autoimmune disorders, etc.

'Typical' optic neuritis characteristically occurs in young Caucasian adults with unilateral mild-to-moderate visual loss, which is associated with mild pain especially on eye movement. The optic discs are usually normal (retrobulbar optic neuritis) but can also be swollen. Gradual (complete/incomplete) recovery of vision is expected within the following few weeks with or without corticosteroid treatment.

'Atypical' optic neuritis stereotypically occurs in non-Caucasian (e.g. Asian, African) of older or paediatric age group, presenting with bilateral/unilateral severe visual loss without

spontaneous recovery after weeks. It can be painless or very painful, waking the patient up from sleep or lasting over weeks. Disc swelling is often severe, with other signs such as marked retinal exudates, macular star, signs of ocular inflammation, or associated with marked disc hemorrhages. After steroid treatment, visual recovery is either very rapid or does not commence even after one to two weeks.

With that in mind, however, the distinction between 'typical' and 'atypical' optic neuritis is not always clear-cut. Atypical factors (atypical patient demographics, clinical features or disease course) should alert clinicians to important underlying conditions that would warrant further workup.

Clinical Presentation

Acute (over hours) or subacute (over days) diffuse or central visual loss is often the presenting symptom in patients with optic neuritis. The severity of visual loss can range from very minimal blurring to no light perception, although mild to moderate visual loss is the commonest (64% of adult eyes from the ONTT had initial acuity better than 6/60[27]). Bilateral simultaneous (within 2 weeks of the onset of the fellow eye) involvement can occur. This is believed to be more common in children.

Visual loss severity tends to reach its nadir within the first two weeks of symptom onset[28] while recovery typically begins within the first few weeks of symptom onset. The recovery is more rapid initially, followed by phase of slow improvement that can continue for months and up to a year after onset, with more than 90% of patients showing visual acuity recovery of 20/40 or better.[29, 30] Progression of visual loss for a longer period of time can occur but should alert the clinician to an alternative diagnosis

Pain in or around the eye is another major symptom of optic neuritis. In the ONTT, pain was reported by 92% of patients, amongst whom 87% indicating that it was worsened by eye movement. The pain is usually mild and lasts no more than a few days.[12]

Other described symptoms include the presence of phosphenes/photopsia (bright, fleeting flashes of light which can be precipitated by eye movement or certain sounds, reported by 30% of the patients in the ONTT); Uhthoff's phenomenon (worsening of vision provoked by rise in body temperature); and the Pulfrich effect (anomalous stereoscopic perception of objects in motion due to asymmetrical conduction between optic nerves).[28]

There are a few particular clinical characteristics in paediatric optic neuritis.[31] The presentation is commonly painless (only 50% with pain[32]) and bilateral (72% for children under 10[17]), often with disc swelling (up to 73%[16, 33, 34]). The visual loss is more severe, and often develops after a preceding viral illness or vaccination (up to two-thirds of younger children reporting an antecedent viral illness[16]). The chance of MS development is lower. It is more steroid-sensitive (and steroid-dependent).

Clinical Assessment

Optic nerve status should be assessed during clinical examination using parameters such as visual acuity, pupillary reaction, color vision, visual field and optic disc morphology.

The distant visual acuity should be documented on every visit using a Snellen chart, ideally with spectacle correction for best-corrected visual acuity (BCVA). It is rare for preverbal children (around <2 years of age) to have optic neuritis, but younger children (2-5 years of age) may need other special tests for visual acuity (e.g. Cardiff acuity cards for 2 years or older; Kay pictures for 3 years or older).

Relative afferent pupillary defect (RAPD) is of paramount importance, and often it is the only clinical sign detected in acute retrobulbar optic neuritis, as the optic disc appearance is normal (hence the idiomatic phrase of "the doctor sees nothing, the patient sees nothing"). In the event of bilateral involvement, however, RAPD can be less obvious or even absent.

Color vision impairment (dyschromatopsia) is often disproportionate to the drop of visual acuity. Tests with pseudo-isochromatic plates (e.g. Ishihara color vision test) can be conveniently performed in the clinic. The number of plates failed can be used as a semi-quantitative indicator of optic nerve function. Patients with visual acuity worse than 6/18 may fail the test even if color vision is relatively well preserved. The first plate (test plate) of the Ishihara chart is used as to assess if a patient has sufficiently good visual acuity to perform the test, and even a color-blind individual would pass. Red desaturation is a subjective measurement of optic nerve function, yet in patient with mild color vision impairment, it might be more sensitive than Ishihara color vision test. A bright red object is shown to each eye separately. The perception of "redness" is subjectively compared to the fellow normal eye, giving a score out of a scale of 1-10 or in terms of percentage.

The optic disc can be normal, swollen or atrophic. In the ONTT, optic disc swelling was observed in 35% of the patients.[12] Disc swelling, which indicates the involvement of the anterior part of the optic nerve (i.e. papillitis), is more common in children (up to 73% of children with optic neuritis[16, 33, 34]) and in Asian patients[35, 36]. Optical coherence topography (OCT) of the peripapillary retinal nerve fiber layer (pRNFL) could identify subtle swelling in clinically normal discs. Optic disc pallor may indicate either previous attack (symptomatic or asymptomatic) or on-going chronic optic neuritis.

A complete ophthalmic examination is required to exclude other causes of visual loss (or optic nerve dysfunction), such as posterior scleritis, uveitis and various causes of retinopathy. Retinal periphlebitis is occasionally observed and was reported to be associated with an increased risk of MS conversion.[37] Uveitis (particularly intermediate uveitis) is associated with multiple sclerosis.[38, 39] Other cranial nerve dysfunction, proptosis, anisocoria, ptosis, etc could point towards other aetiologies and therefore should be actively assessed.

Investigations

The diagnosis of optic neuritis is clinical, but investigations are needed to classify the disease, monitor the optic nerve functions and rule out other differential diagnoses in atypical cases.

MRI of the brain and orbits with and without gadolinium contrast is the imaging modality of choice for patients presenting with optic neuritis. The typical findings

of hyperintense signal along the optic nerve in T2-weighted sequence and contrast enhancement in T1-weighted fat suppression sequence are indicative of optic neuritis. In the presence of optic atrophy, the increased cerebrospinal fluid (CSF) space around the atrophic optic nerve would show T2-weighted hyperintense signal and might be mistaken for active optic neuritis. The absence of contrast enhancement can help distinguish optic neuritis from active optic neuritis and unnecessary treatment may be avoided.[40] The sensitivity of MRI in the diagnosis of optic neuritis was reported to be 94% (all cases had the MRI scan prior to treatment and within 20 days of symptom onset; using 1.5 T MRI unit with 3mm thick slices, 0.3 mm spacing).[41] If signs and symptoms of myelitis are present, MRI study of the spine should also be performed. Although not diagnostic on their own, specific MRI findings could be valuable for clinicians to reach the exact diagnosis and for prognostication. These were included in the respective diagnostic criteria for CIS/MS (adult/paediatric), NMOSD, ADEM, etc.[42-44]. In the ONTT, the risk of MS after optic neuritis is related to the MRI findings at study entry. The cumulative risk of MS was 25% at 15 years of follow-up in patients without any MRI lesions. The risk was increased to 60% if there was one lesion (Hazard Ratio [HR] 2.80 (1.68-4.68) compared to no lesions) and increased to 78% (HR 4.46 (2.99-6.65)) if there were three or more lesions on MRI.[45]

Lumbar puncture is not essential in isolated optic neuritis, although surveillance for MS might be modified by the presence of OCBs[18], particularly in children as they were found in 80% of pediatric patients with MS and in only 15% of children with monophasic optic neuritis.[46] In the presence of polyfocal white matter disease or atypical features that are suggestive of alternative diagnosis, lumbar puncture should be performed for the OCBs, paired protein and glucose levels, and cell count. If CNS infection is suspected, viral polymerase chain reaction and microbial culture should be performed.

As paediatric optic neuritis is more commonly in the form of bilateral disease with disc swelling, idiopathic intracranial hypertension is a differential diagnosis especially if the chronicity is not clear from history. CSF opening pressure, however, may not help to differentiate between the two as intracranial pressure may be elevated in the event of cerebral inflammation[47, 48] and/or due to raised pCO2 during sedation without respiratory control.[49]

Blood tests should be directed towards underlying aetiologies, and to ensure safety in administration of corticosteroid. Basic blood tests commonly ordered by the authors for Hong Kong adults patients include hepatitis serology, syphilis serology, inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), complete blood count and liver/renal biochemistry. Autoimmune markers (antinuclear antibody, antineutrophil cytoplasmic antibodies, etc) should be checked judiciously in the presence of relevant systemic features of autoimmune disorders/vasculitis. In cases with bilateral or rapidly sequential disease responding poorly to treatment, particularly when MRI is not readily available during the acute phase, Leber's hereditary optic neuropathy (LHON) mitochondrial DNA analysis should be considered in suspected patients.[50]

Chest radiograph should be done for to rule out active pulmonary tuberculosis infection in endemic areas (e.g. Southeast Asia) and to look or features suggestive of sarcoidosis, although sarcoidosis is uncommon in the local population. If the optic neuritis appears to

be steroid-dependent, blood tests for serum angiotensin converting enzyme should also be considered.[51, 52]

AQP4-IgG is important in the diagnosis of NMOSD.[43] From immunopathogenesis studies, it is an autoantibody that targets the water channel aquaporin-4 on the astrocytic membrane in the central nervous system (CNS), leading to astrocyte death and reactive gliosis.[53] As such, it is different from MS in that it is not a disease that primarily affects myelin, but an astrocytopathy with secondary axonal loss. The specificity and sensitivity of the test in the diagnosis of NMO is approaching 100% (false positive rate of 0.1% by cell-based assay was reported)[54] and 70-80% respectively.[55]

MOG-IgG targets MOG, a membrane protein expressed on the surface of oligodendrocyte and on the outermost surface of myelin sheath.[56] Unlike AQP4-IgG which is pathogenic, the role of MOG-IgG in pathogenesis is yet to be determined. It was reported to be positive in patients with clinical characteristics of NMOSD but negative AQP4-IgG (i.e. seronegative). Compared to NMOSD, this related but distinct subgroup of patients are younger, with lower female to male ratio, and less likely to relapse (yet most patients still run a relapsing course)[57-59]. In paediatric patients with positive MOG-IgG, the commonest phenotype was reported to be monophasic ADEM, typically after a viral illness or vaccination.[60] Optic neuritis (bilateral more than unilateral) was the predominant phenotype in adults, although smaller proportion of paediatric patients also presented with optic neuritis.[58-60]

Optical coherence tomography (OCT) is a non-invasive, quick and reproducible imaging modality important in many aspects of ophthalmology. Analysis of the pRNFL thickness in a near-histology resolution can detect even subtle optic disc swelling or atrophy, and allows monitoring of disease progression. That being said, during the acute phase of retrobulbar optic neuritis, the OCT pRNFL thickness can be deceptively normal as the secondary atrophic changes can take up to two to three months to manifest. In cases with disc swelling, the pRNFL thickness is increased due to oedema, thus it cannot be used to reflect axonal loss. At this stage, macular ganglion cell-inner plexiform layer (GC-IPL) thickness analysis, which is not affected by disc swelling, may be used instead, although GC-IPL measurement in the setting of acute disc swelling is more prone to measurement error.[61]

Visual field testing can be performed using kinetic (mapping visual field using stimulus of known luminance moving from a non-seeing area to a seeing area) or static (stimulus is stationary with varied intensity until the sensitivity at that point is found) perimetry. In the ONTT, it was shown that variable patterns of visual field defect were possible – diffuse and focal defects such as central, centrocaecal, altitudinal, arcuate, nasal step, and even hemianopic defects.[12] Although kinetic perimetry has the advantages of testing a wider field and allowing direct observation of eye fixation during the test, static perimetry allows a more quantitative assessment that can be used for longitudinal follow-up. The latter can also map scotomas (focal defects) more readily. Regardless of the type of test employed, visual field testing requires patient cooperation. There were studies looking into the feasibility of visual field testing in children using different test strategies and showed that even young children could give meaningful results.[62-64] In real life, whether visual field can be used to monitor a paediatric patient with optic neuritis should be determined on a case-by-case basis

Visual evoked potential (VEP) is a gross electrical response recorded from the visual cortex in response to a visual stimulus in the form of flash (flash VEP) or pattern (PVEP). Flash VEP can be performed in young children (or even infants) under sedation using a handheld Ganzfeld stimulator. It may indicate whether a response is present or not, but it cannot quantify the response since a local normative database is unavailable. In unilateral disease, the response of the affected side can be compared to the other side.

PVEP is preferrable to flash VEP as it provides more information from the P100 (the positive deflection that occurs at about 100ms) amplitude and peak latency. As a rule of thumb, the amplitude is reduced in axonal degeneration and peak latency is prolonged in demyelination, although some degree of overlap usually exists. It is quantitative and can be used for estimation of visual acuity. However, it is highly dependent on patient cooperation, hence less suitable for young children. Achieving accurate PVEP is also reliant on correction of the patient's refractive errors when performing the test, which may be difficult to achieve in a neurology practice.

Treatment (see Figures 1 & 2)

Treatment of acute exacerbations

In typical optic neuritis, there is generally good recovery of visual functions with or without corticosteroid treatment; atypical optic neuritis, on the other hand, can lead to profound irreversible visual loss without prompt treatment. During the initial presentation of an isolated optic neuritis, when it is not yet clear whether it is typical or atypical, a course of corticosteroid should be considered, unless there is any suspicion of an underlying infective aetiology and/or presence of corticosteroid contraindications. Observation may be suitable for optic neuritis cases where the visual functions are very minimally affected and/or the symptoms are already spontaneously on an improving trend; yet close monitoring is still warranted.

The corticosteroid regimen, as studied in the ONTT, has been the standard of treatment for *adult acute typical optic neuritis*. Intravenous administration of methylprednisolone (250mg every 6 hours) for three days followed by oral prednisone (1 mg/kg per day) for a total of two weeks has been proven to hasten visual recovery, yet the visual outcomes at 6 months were not altered.[65, 66] The onset of clinically definite MS at two years was delayed[67], but such effects diminished over time.[45] Oral prednisone alone (1 mg/kg per day) should be avoided since it is associated with higher rate of recurrence as shown in the ONTT. The reason for this observation was unclear. Interestingly, the PVEP and visual acuity of patients receiving intravenous methylprednisolone (1000 mg per day for three days) and the bioequivalent oral dose (1250 mg prednisone for three days) were comparable, suggesting that the difference between the intravenous and oral routes detected in the ONTT could have been a matter of dosage difference.[68]

Monitoring of the response to steroid is important to guide the next step. Patients with typical optic neuritis classically show visual recovery gradually over the following few weeks. Clinical course that deviates from that of typical optic neuritis towards the two extremes (*i.e.* drastic recovery or lack of improvement) upon corticosteroid treatment

is an atypical feature. For poor responders, therapeutic plasma exchange (TPE)[69-76] and intravenous immunoglobulin (IVIg)[69, 72, 77-81] could be considered in addition to corticosteroid as second-line agents, in cases where NMO is suspected/confirmed and especially when visual loss is severe, in order to salvage the optic nerve functions. For good responders, relapse should be watched out for when corticosteroid is being tapered off, as inflammatory optic neuritis tends to be steroid-dependent as well as steroid-responsive. Slow tapering of corticosteroid over several months is suggested for atypical and inflammatory optic neuritis.[28, 82, 83]

In Hong Kong where the majority of the population is Chinese (in contrast to the ONTT population with 85% of subjects being Caucasian[12]), clinicians should be aware of the higher likelihood of atypical optic neuritis.[84] Indeed, it was reported that up to 17% of optic neuritis in Hong Kong were associated with NMOSD.[85]

No clinical trial has been conducted for PON. The rationale of corticosteroid treatment in PON has largely been extrapolated from the ONTT. The regimen is intravenous methylprednisolone (20-30mg/kg/d, maximum dose of 1g/day) for three to five days, followed by oral prednisolone which is to be tapered over 2 weeks.[18, 86-89]

Prevention of relapse

As recovery from optic neuritis may not be complete (and often limited), relapse prevention is crucial. Patients with MS should be assessed by neurologists for disease-modifying treatments (DMTs). It is worth noting that certain DMTs used for MS, such as interferon-beta[90-93], natalizumab[94-96] and fingolimod[97], were reported to increase the rate of relapse in NMOSD, due to differences in pathogenesis. Recurrent inflammatory type of optic neuritis (*i.e.* steroid-responsive) should receive treatments with immunosuppressive agents.

A representative condition of this kind is optic neuritis associated with NMOSD, which tends to run a stepwise downhill course with accumulated disability without immunosuppression. Azathioprine[98, 99], mycophenolate mofetil[100, 101] and rituximab[102] were effective in reducing the relapse rate. Intravenous eculizumab was shown in seropositive patients to significantly reduce the relapse rate, albeit with concerns of meningococcal infection.[103]

Summary

Optic neuritis is an important cause of visual loss, ranging from a self-limiting, monophasic, idiopathic and isolated condition, to one that is disabling, recurrent and associated with underlying systemic neurological disorders. The advent of neuro-imaging and various laboratory tests has facilitated the classification of optic neuritis. Distinction between typical and atypical optic neuritis is important for guiding investigation and treatment. Clinicians should be aware of the differences in clinical presentation, response to corticosteroid treatment, risk of relapse, association with systemic neurological disorders in "atypical patients" such as the local Chinese population and paediatric patients.

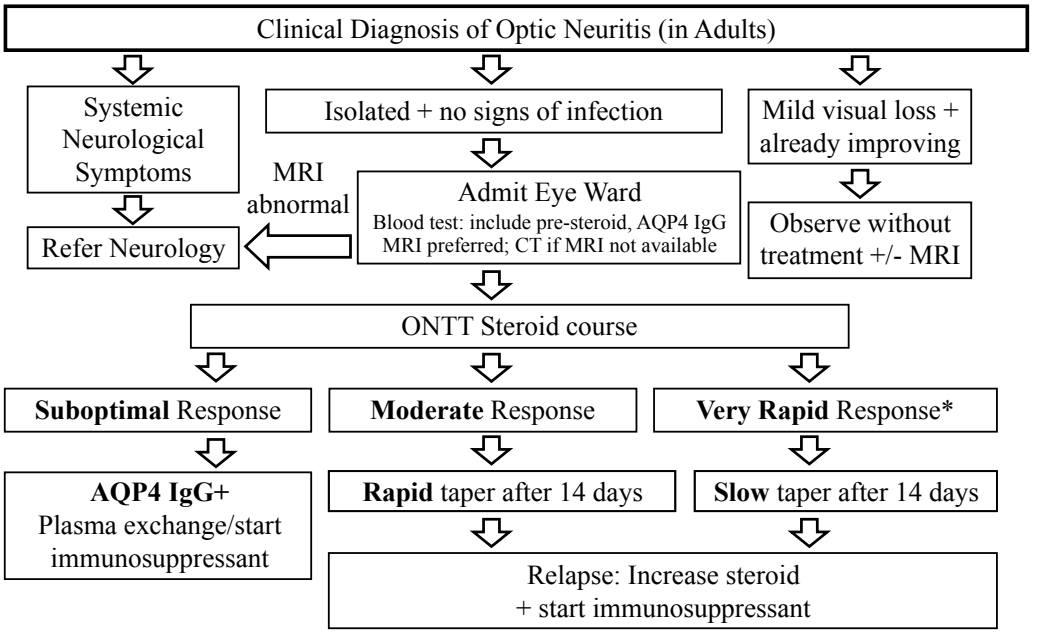

Table 1. Management of optic neuritis in adults in Hong Kong
*especially if positive for AQP4 IgG.
AQP4, aquaporin-4; CT, computed tomography (of the brain and orbits with iodinated contrast); MRI, magnetic resonance imaging (of the brain and orbits with and without gadolinium contrast); ONTT, Optic neuritis treatment trial (see text for steroid regime)

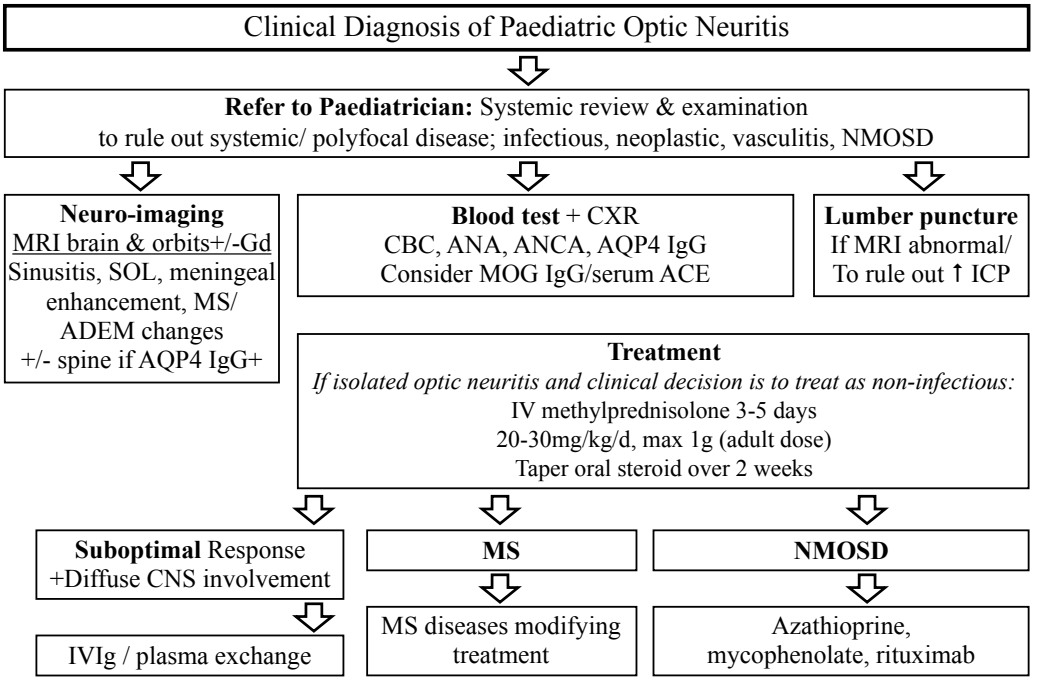

Table 2. Diagnosis and management of paediatric optic neuritis
ACE, angiotensin-converting enzyme; ADEM, acute disseminated encephalomyelitis; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; AQP4, aquaporin-4; CXR, chest radiograph; CBC, complete blood count; ICP, intracranial pressure; IVIg, intravenous immunoglobulin; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; SOL, space-occupying lesion;

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Multiple Sclerosis in Hong Kong

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Multiple Sclerosis (MS) is a central nervous system demyelinating disease that mainly affects the brain, spinal cord and optic nerves. Although its exact pathology remains uncertain, it is widely accepted to be auto-immune in origin. Repeated inflammation led to the formation of scar tissues, or better known as MS plaques, which resulted in disability as time went on.

With heightened awareness and greater availability of neuro-imaging, the prevalence of multiple sclerosis has steadily risen over the past decade in Hong Kong. As of 2015, MS affects 6.8 per 100,000 people in our local population, and it is estimated that approximately 500 MS patients are currently under care of the Hospital Authority (HA).

The majority of patients suffers from the relapsing-remitting form of MS (RRMS), while a smaller proportion has progressive disease, either primary progressive (PPMS), or secondary progressive (SPMS). Before 2012, treatment was only available for RRMS patients in the form of beta-interferons. However, they were either self-financed or funded under HA safety net.

In 2012, beta-interferons became a special drug in the HA formulary, and the HA MS Expert Panel was formed, comprising of MS specialists from adult and paediatric neurologists. The panel was responsible for endorsing the use of beta-interferons in relapsing remitting MS cases, as well as vetting applications for the Samaritan-funded second line drugs Fingolimod and Natalizumab, which became available in 2013 and 2015 respectively. In 2017, two oral first line agents, Teriflunomide and Dimethyl Fumarate were approved as HA special drugs. A third line agent, Alemtuzumab, became available as a self-financed or funded item in 2018, and Fingolimod also became a special drug in 2019. All of these advancements gave us physicians more tools to help our MS patients improve disease control.

The Hong Kong Multiple Sclerosis Society (HKMSS), a local charitable and academic organization, was established in 2012 under the chairmanship of Dr. Koon-Ho Chan. The society council currently consists of 11 members, and aims to promote awareness of MS in our community; help patients gain early access to early diagnosis and treatment; alleviate the disease burden on their daily lives; and help patients and their carers live a full life.

In order to encourage knowledge exchange, the HKMSS organizes regular scientific meetings, and we were honoured to have received talks from many internationally renowned top experts in the field since our establishment. The society also collaborates with various organizations to host health talks, press conferences, and publish media articles to arouse the public and government's awareness to MS. In 2019, to commemorate the annual World MS Day, which was themed #MyInvisibleMS, we have organized our first ever

patient-centered event, a workshop to help participants learn and become more in tune with their bodies despite the physical disabilities.

Thanks to the availability of more disease modifying agents and the combined efforts of our local MS healthcare experts, we are happy to see that MS care in Hong Kong is catching up with international standards. In fact, in addition to MS, there is also great advancement in two other closely related central nervous system inflammatory diseases, namely Neuromyelitis Optica Spectrum Disorders (NMOSD) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) syndromes.

Since the discovery of the anti-aquaporin-4 (AQP4) antibody in 2004, many patients once thought to suffer from an opticospinal form of MS were found to have NMOSD instead, which predominantly affects the optic nerves and the spinal cord. Over the years, the definition of NMOSD has undergone several revisions, and we now know that NMOSD patients may also have brain lesions. In recent years, some seronegative NMOSD patients were found to have the anti-MOG antibody, and at the time of writing, there is still no universal consensus on whether it is a subtype of NMOSD or a completely distinct entity.

Nevertheless, these two antibodies were important because treatment of NMOSD and anti-MOG syndromes was vastly different from MS. Disease modifying drugs that target MS are ineffective or even harmful in NMOSD and anti-MOG syndromes. The anti-AQP4 antibody test has been made accessible in the Hospital Authority by Queen Mary Hospital Immunology laboratory several years ago, and since 2018, the anti-MOG antibody test also became available. Having access to these two tests allowed us to make more precise diagnoses, and ensure that patients receive the appropriate treatment.

Speaking of treatment, until 2019, all the agents used to treat NMOSD, including Azathioprine, Mycophenolate Mofetil, or even Rituximab, were off-label. However, this year, Eculizumab, an anti–complement C5 monoclonal antibody, became the first ever drug approved for treatment of NMOSD by the U.S. Food and Drug Administration (FDA). Two other agents, Satralizumab and Inebilizumab were also found to significantly reduce relapse rates in NMOSD. While these three agents are currently not available in Hong Kong, it is something to look forward to, and we hope that they would become accessible to our local patients in the near future.

Finally, I would like to take this opportunity to thank the Hong Kong Society of Child Neurology and Developmental Paediatrics (HKCNDP) for inviting me to write this article on behalf of the HKMSS. It is my hope that there will be even closer collaborations in the future between all important stakeholders of MS care in Hong Kong, which certainly include paediatric colleagues. Do visit our society website at www.hkmss.org and join us to become a member!