Neurology Asia 2014; 19(1) : 37 – 46

Relapsing inflammatory demyelinating syndromes amongst children in Borneo

Terrence Thomas *MRCPCH*

Neurology Service, Department of Paediatrics, KK Women's and Children's Hospital, Singapore; Neurology Service, Department of Paediatrics, Sabah Women & Children's Hospital, Kota Kinabalu, Malaysia

Abstract

We present a case series of children with relapsing inflammatory demyelination who live on the island of Borneo, a relatively rural region of South East Asia with a warm, tropical climate. The four cases are a 9 year old girl with a polyfocal clinically isolated syndrome who had a single recurrence of symptoms soon after completing steroid taper, a 6 year old boy with relapsing-remitting multiple sclerosis (MS), an 8 year old boy with relapsing neuromyelitis optica and an 8 year old boy with chronic recurrent optic neuritis (CRION). The clinical presentation and neuroimaging features in our children are similar those seen in children living in temperate world regions. The new recommendations by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) in classifying childhood inflammatory demyelinating disorders are useful in our children. This report hopes to raise awareness of relapsing inflammatory demyelinating syndromes in children living in a region with a low risk for MS.

INTRODUCTION

We report a selected case series of relapsing inflammatory demyelinating disorders in children living on the island of Borneo – a tropical island in South East Asia.

Monophasic inflammatory demyelination syndromes are not uncommon amongst children living in South East Asia. Children presenting with a first acute demyelinating syndrome (ADS) episode are classified as having either a clinically isolated syndrome (CIS) or acute demyelinating encephalomyelitis (ADEM), with encephalopathy the defining feature in ADEM.[1,2] New recommendations by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) describe a CIS/ADEM episode based on clinical symptomatology as either a *monofocal* or *polyfocal* event occurring in one or more areas of the brain, optic nerves or spinal cord.

This report hopes to raise awareness of relapsing inflammatory demyelinating syndromes in children amongst pediatricians and primary care practitioners living in this region. Children with relapsing disease typically have either multiple sclerosis (MS) or relapsing neuromyelitis optica (NMO); relapsing transverse myelitis and chronic recurrent inflammatory optic neuritis (CRION) are rare.

CASE REPORTS

Patient 1. Polyfocal clinically isolated syndrome, with a recurrence

A 9 year-old ethnic Kadazan girl first presented with bilateral visual loss (Acuity < 6/60, only able to count fingers, over both eyes) and mild left thigh weakness over 3 days, following an upper respiratory tract infection. On examination, she also had impaired vibratory sense and joint position at both toes. MRI studies of the brain, spinal cord and orbits showed focal areas of acute demyelination in the right motor cortex (medial convexity), dorsal column at the C4-5 cervical region (Figure 1, Plates A-D) and swollen optic nerves. She was treated with IV methylprednisolone 30mg/kg/day for 5 days, followed by a slow taper of oral prednisolone over 6 weeks. By the end of the steroid taper, she had regained visual acuity (right eye 6/18, left eye 6/12) with near-normal colour perception, and demonstrated full motor power over the left lower limb and normal thresholds to vibratory sense.

A week after cessation of steroids, she again experienced sudden bilateral visual loss (Acuity < 6/60, left eye only sees hand motion; right eye is able count fingers close to the eyes) and a more pronounced left lower limb weakness

Address correspondence to: Terrence Thomas, Consultant, Neurology Service, Department of Paediatrics, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899. Email: Terrence.Thomas@kkh.com.sg

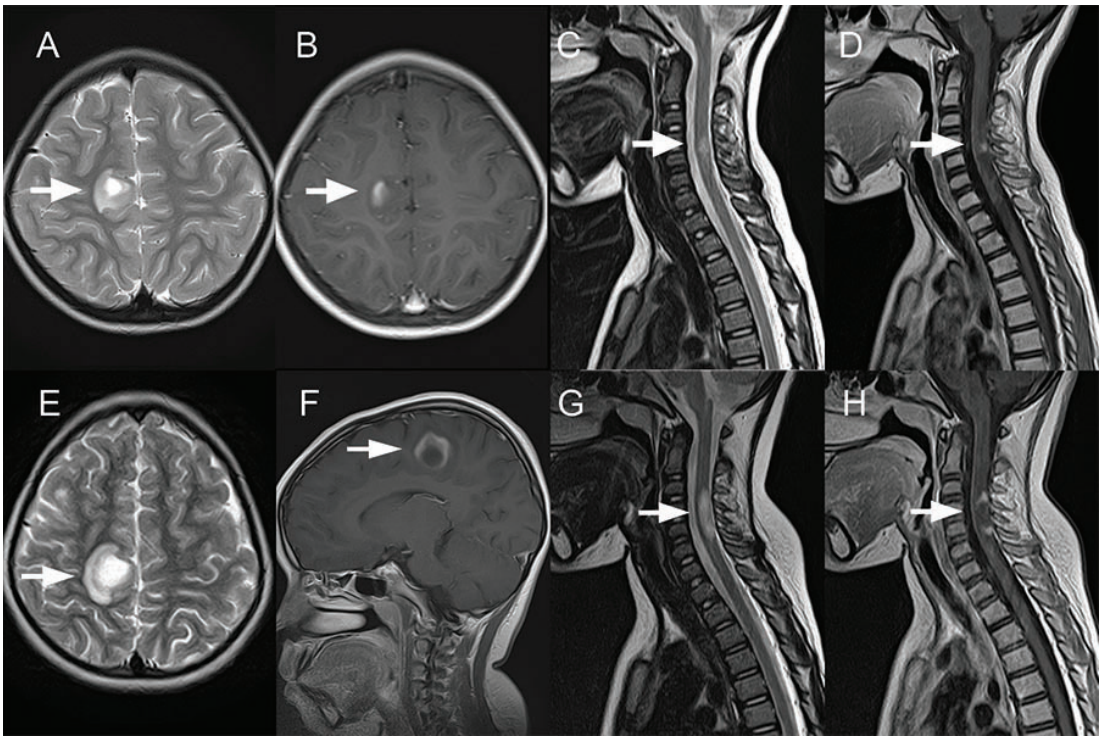

Figure 1. MRI images in Patient 1 during her first presentation with bilateral visual loss, left thigh weakness and impaired proprioception in both distal lower limbs. Axial T2-weighted FSE (A) and axial T1-weighted FSE with gadolinium (B) brain images showing a focal area of acute demyelination (white arrow) in the right pre-central gyrus, medial convexity, i.e. corresponding to the motor cortex for control of the left lower limb. Sagittal T2-weighted FSE (C) and Sagittal T1-weighted FSE with gadolinium (D) of the cervical spinal cord showing a focal area of acute demyelination (white arrow) in the posterior cord (posterior column) at C4-5 region.
Plates E-F. MRI images in Patient 1 when she presented with a recurrence of her symptoms 2 months from initial illness, following cessation of steroid treatment. Axial T2-weighted FSE (E) and sagittal T1-weighted FSE with gadolinium (F) brain images showing a larger area of focal demyelination (white arrow) in the right pre-central gyrus, medial convexity. Sagittal T2-weighted FSE (G) and Sagittal T1-weighted FSE with gadolinium (H) of the cervical spinal cord showing a more clearly defined posterior cord lesion at the C4-C6 region (white arrow). In both these lesions the contrast enhancement is more exuberant.

(MRC scale 3/5 over the left hip flexor) than in her first presentation. Again, she had increased thresholds to vibratory sense and joint position at both toes. Repeat MRI imaging studies (Figure 1, Plates E-H) showed more exuberant areas of acute demyelination in the previously affected brain and spinal cord areas, but no new areas of involvement. She improved with a second pulse of IV steroids followed by a prolonged taper over 6 months. MRI imaging of the brain and spine a year after the recurrence is normal and she has since had no new symptomatology over the past 4 years. She has no residual disability and retains normal visual acuity (6/6) and colour perception.

Patient 2. Relapsing-remitting Multiple Sclerosis

A 6 year-old ethnic Chinese boy was first seen by a paediatric ophthalmologist for right optic neuritis. He had been previously well, and had presented acutely with pain on right eye movements and sudden loss of vision (6/60 acuity) in the right eye. On brain imaging, there were new and old demyelinating lesions (Figure 2A). Cerebrospinal fluid examination showed normal protein and white cell counts, but was negative for oligoclonal bands (by protein electrophoresis). As a surveillance MRI three months later showed new asymptomatic lesions in the right parietal lobe and left centrum semiovale (Figure 2B),

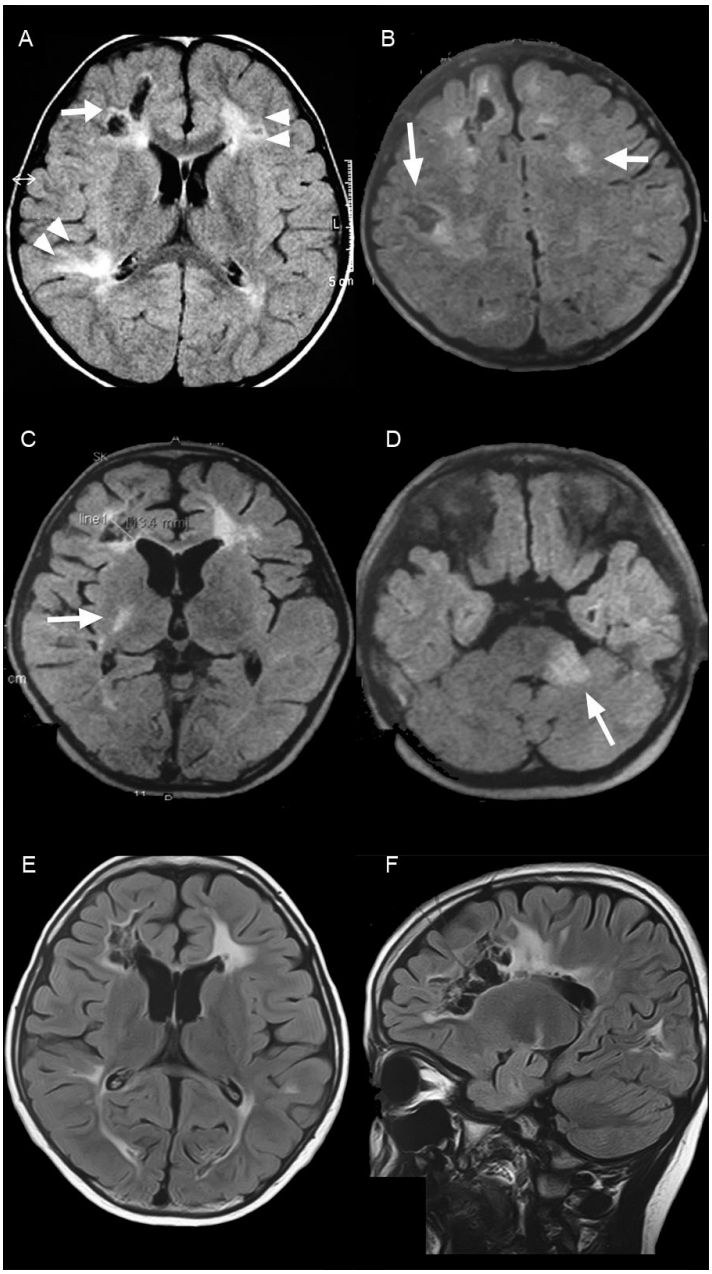

Figure 2. Serial MRI brain images from a 6 year old boy with relapsing-remitting multiple sclerosis. (A). First presentation with optic neuritis, but no symptoms referable to the central nervous system. Axial T2 FLAIR brain image showing two hypointense "black holes" in the right frontal region (white arrow) and hyperintense demyelinating lesions (arrowheads) over the left frontal and bilateral parietal-occipital periventricular region. (B). Surveillance MRI study at 3 months. He was asymptomatic at this time. Axial T2 FLAIR brain reveals multiple new white matter lesions in the right parietal lobe and left centrum semiovale (white arrows).
(C), (D). Serial MRI axial T2 FLAIR brain scans at different time points in the 3 years of frequent relapses showing new symptomatic lesions in the right internal capsule (clinical left hemiparesis) (C) and left cerebral peduncle (clinical right hemiparesis) (D). (E), (F). Surveillance MRI during a quiescent, asymptomatic phase following pulsed cyclophosphamide therapy. Axial and sagittal T2 weighted brain images showing accumulation in white matter injury over time – extensive hyperintense white matter lesions with larger areas of axonal loss ("black holes").

he was started on SC interferon beta-1a 22mcg thrice weekly. Despite treatment with disease modifying drugs, he experienced five relapses – two multifocal brain and brain/eye CIS (ataxia, right hemiplegia, right hemianaesthesia; left optic neuritis, ataxia), two monofocal brain CIS (left hemiplegia; right hemiparesis) and one monofocal spinal cord CIS (paraplegia with urinary incontinence), over the next 3 years (Figure 2 C,D). Each relapse was treated with pulsed IV methylprednisolone followed by a prolonged taper with oral prednisolone. To stabilize his disease, he was given 6 pulses of IV cyclophosphamide 800mg/m^2, every month. Following this, he had only one brain relapse (monofocal brainstem – isolated opsoclonus) over the subsequent 4 years. He is currently 13 years of age, and retains independent mobility. He requires a magnifying glass for reading, has poor colour perception and has learning disability. Follow up brain MRIs (Figure 2 E,F) show mild cerebral atrophy (prominent sulci, mild ventriculomegaly), cavitating "black holes" and accrual of white matter scarring from relentless disease.

Patient 3: Relapsing neuromyelitis optica

An 8 year old ethnic Brunei Malay boy first presented at age 4 years with a 2 day history of gradual walking difficulty and urinary incontinence. He had a sore throat in the previous week, but reported no preceding fever or trauma. On examination he was alert and well orientated, had normal visual acuity, brisk symmetrical pupillary reflexes and normal fundoscopy. He had normal upper limb strength and tendon reflexes but flaccid weakness over both lower limbs, bilateral extensor plantar responses and a sensory loss from the T10 dermatome downwards. The urinary bladder was grossly distended.

MRI spine showed longitudinally extensive transverse myelitis (LETM) extending from C6 to T8 (Figure 3A). Brain MRI was normal. He received both IV immunoglobulins 2g/kg, 5 days of IV methylprednisolone 20mg/kg/day and then oral prednisolone for the subsequent 2 weeks. Spinal fluid testing showed normal biochemistry, lymphocytosis (40 cells/mm^3), no red blood cells and no oligoclonal bands. Antinuclear factor was negative, as was serological testing for Epstein Barr virus and *Mycoplasma pneumoniae*. He slowly regained ambulation and sensory function over 4 weeks. Bladder recovery was less impressive, as he needed clean intermittent urinary catheterization for 5 months.

Eight months from his first illness, he developed acute blurring of vision (only light perception, unable to count fingers; acuity < 6/60) in the right eye over 2 days. Examination showed right optic disc oedema and prolonged P100 latencies on visual evoked potentials were demonstrable in the right eye. He was given IV methylprednisolone

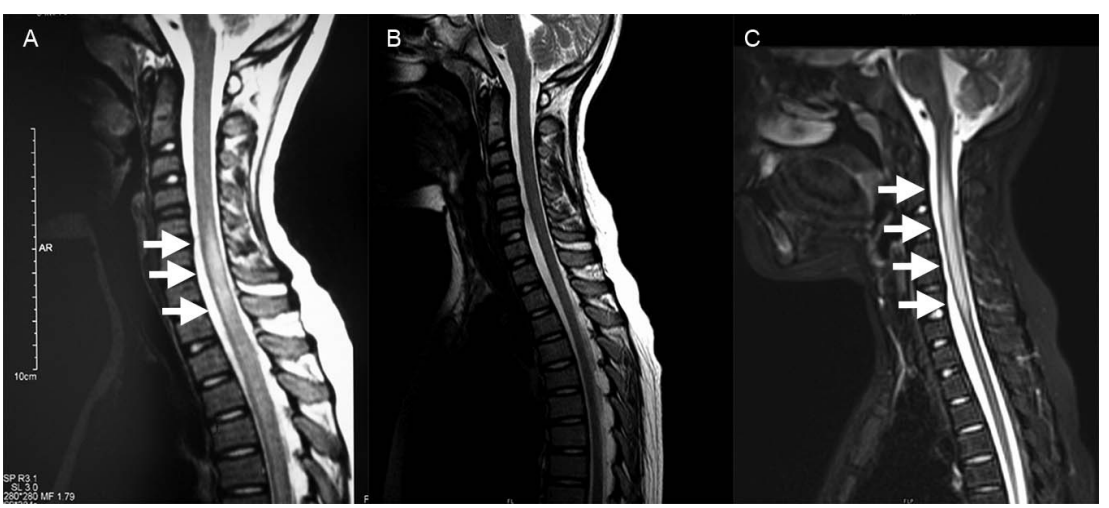

Figure 3. Serial sagittal T2 weighted MRI spinal cord images from an 8 year old boy with relapsing-neuromyelitis optica. (A), longitudinally extensive spinal cord lesion extending from C6-T8 vertebral region (white arrows), during his first presentation. (B), the spinal cord appears normal during his first relapse, an isolated optic nerve presentation, at 8 months from first disease. (C), a contiguous spinal cord lesion extending from C3 –T1 vertebral levels during a spinal cord relapse a year later.

30mg/kg/day for 5 days followed by a two-week taper of oral prednisolone. His vision gradually improved over 3 months, with complete return of full (6/6) visual acuity and colour vision.

In the next year, he develops a second spinal cord presentation (neck pain, upper limbs weakness; cervical spine involvement on MRI (Figure 3C) and isolated left optic neuritis (acuity 6/60). Both episodes improved with IV steroids but and a longer oral taper.

He was then transitioned on to long term immunomodulatory therapy with azathioprine 2mg/kg/day and has done well since. Five years on, he has no visual, motor or urinary disability; brisk lower limb reflexes are still demonstrable on physical examination.

Patient 4. Chronic recurrent inflammatory optic neuritis (CRION)

An 8 year-old boy of mixed Indian and Malay ethnicity presents with acute, near-complete visual loss (acuity < 6/60, perceives hand motion) and colour desaturation over the right eye, occurring one week after a viral illness. He was treated by an ophthalmologist, and made a complete recovery with IV methylprednisolone 20mg/kg/day and a 2-week course of oral prednisolone.

Two years later he developed a sudden loss of visual acuity (again < 6/60, only perceiving hand motion) and colour desaturation over the same eye. He had headache, but reported no prodromal illness. The neurological examination was completely normal. Brain imaging and spinal fluid examination were normal but there were absent responses on visual evoked responses over the right eye. He gradually improved with IV methylprednisolone 1 g daily for 5 days followed by a 2-week taper of oral prednisolone.

During the second episode, blood and CSF investigations for infections, autoimmune disorders, malignancy and a metabolic screen was normal (as in Table 1). Visual evoked responses were normal with 6/6 visual acuity over both eyes at six months from illness. Four years on, he remains well with no further relapses and normal visual acuity.

DISCUSSION

Relapsing demyelinating disorders are known to occur in children living in Asia, though reports in the literature are few and limited to hospitals in cities and large urban centres.[3-6] This report presents a selection of patients living on the island of Borneo - a relatively less developed and rural environment. The range of relapsing inflammatory demyelinating syndromes in our patients is similar to those seen in children living in temperate world regions.[3,7,8]

Risk factors for relapsing demyelination exist in South East Asia. A large prospective Canadian cohort of 302 children followed from a first acute demyelinating syndrome (ADS) identified vitamin D insufficiency and previous Epstein Barr virus (EBV) infection as risk factors towards relapsing inflammatory demyelination.[7] Though South East Asia is a tropical location with constant sun and ultraviolet B radiation throughout the year, up to 70% of urban children living in this region have been shown to have Vitamin D insufficiency.[9] EBV infections are common to South East Asia, as evidenced by the high prevalence of EBV–related diseases: nasopharyngeal carcinoma and Burkitt's lymphoma.[10,11]

Ethnic trends in Asian children with inflammatory demyelinating disorders are not clearly defined. Our patients represent an even spread of ethnicity of children living on the island of Borneo. A recent study in Singapore reports an equal incidence of inflammatory disorders amongst children of different ethnicity.[6]

In all children presenting with what may appear to be relapsing demyelination, it is imperative to first exclude other important and more common diagnoses: herpes virus encephalitis, organic acidemias, leukodystrophy, CNS leukemia or lymphoma, haemophagocytic lymphohistiocytosis, and multifocal glioblastoma multiforme.[12] Table 1 gives a more complete list of differential diagnosis to consider, and a recommendation for screening tests typically used at our institution, which were normal in our four patients.

Patient 1 had a polyfocal clinically isolated syndrome (CIS) rather than acute disseminated encephalomyelitis (ADEM), due to the lack of encephalopathy.[1] The new symptoms following withdrawal of steroids, though more severe, is by definition a *recurrence* rather than a *relapse*, as the deficits are similar to that of the first presentation and no new areas of demyelination are seen on brain and spinal imaging (i.e. there is no dissemination in space).[13] Differentiating a recurrence from a relapse is important as patients with relapsing disease will require long-term immunomodulatory treatments.

Some children with a first ADS episode may have little or no clinical improvement after a course of IV steroids. Commonly used second line treatments in refractory disease are IV

Table 1: Differential diagnosis in children with recurrent or relapsing inflammatory demyelination. The column on the right lists recommended investigations to help look for these conditions.

Differential Diagnosis	Important investigations
Infectious disorders	*Recommended:*
Immunocompetent children:	CSF PCR for TB
Tuberculous meningitis	CSF PCR for herpes simple virus
Herpes simplex encephalitis	Human immunodeficiency virus serology
Neurocysticercosis	Cysticercus serology (if endemic to region)
Immunocompromised children:	*Consider:*
Tuberculous meningitis	TB interferon gamma release assays (IGRA)
CNS toxoplasmosis	CSF PCR for JC virus
Cytomegalovirus encephalitis	
Progressive multifocal leukoencephalopathy (PML)	
Immune disorders	*Recommended:*
Systemic lupus erythematosus	C3, C4 Complement levels
Sjögren's syndrome	Erythrocyte sedimentation rate
Neuro-Behçet's	Anti-nuclear antibody
Wegener's granulomatosis	Anti-double stranded DNA antibodies
Coeliac disease	
Childhood polyangiitis of the CNS (cPACNS)	*Consider:*
	Extractable nuclear antigens (Sjögren's)
	Pathergy test (Neuro-Behçets)
	Anti-neutrophil cytoplasmic antibodies (Wegener's)
	Anti-endomysial, anti-tissue transglutaminase antibodies (coeliac disease)
	Brain biopsy (cPACNS)
Malignancy/lymphoproliferative disorders	*Recommended:*
CNS leukemia	Blood counts, and peripheral blood film
CNS lymphoma	CSF for blasts, and histopathology
Multifocal glioblastoma multiforme	
Haemophagocytic lymphohistiocytosis/ Macrophage activation syndrome (HLH/MAS)	*Consider:*
	Serum ferritin (HLH/MAS disease)
	Bone marrow aspiration
	Brain biopsy
Treatment – related disorders	*Review all prior medications received*
Radiation injury	
Intrathecal methotrexate	
Posterior reversible encephalopathy Syndrome (PRES)	
Genetic-Metabolic disorders affecting white matter	*Recommended:*
Mitochondrial disorders	Serum vitamin B12 levels
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)	Plasma and CSF lactate
	Plasma acylcarnitines
	Urine organic acids
Leukoencephalopathy with brainstem and spinal cord involvement and high lactate (*DARS2* gene)	*After careful consideration of MRI features and results of the above, consider:*
	Plasma homocysteine levels

Differential Diagnosis	Important investigations
	Plasma very long chain fatty acids and phytanic acids (peroxisomal disorders)
Hypomyelinating disorders	MELAS mutation analysis
Alexander disease (AD)	*DARS2* mutation analysis
Pelizaeus-Merzbacher disease (PMD)	*GFAP* mutation analysis (AD)
Leukoencephalopathy with vanishing white matter (VVM)	*PLP1* or *GJA12* mutation analysis (PMD)
	EIF2B mutation analysis (VVM)
Dysmyelinating disorders	*MLC1* mutation analysis (MLC)
Homocystinuria	*NOTCH3* mutation analysis (CADASIL)
Lysosomal storage disorders	*COL4A1* mutations (HANAC)
Metachromatic leukodystrophy	*GJB1* mutations (connexin-32) (CMTX)
Krabbe leukodystrophy	
Vacuolar white matter degeneration	Specific enzyme analysis for leukodystrophies and lysosomal storage disorders as listed in first column
Vitamin B12 deficiency	
Megalencephalic leukoencephalopathy with subcortical cysts (MLC)	
Toxic accumulation with white matter injury or inflammation	
Peroxisomal disorders	
X-linked Adrenoleukodystrophy	
Organic acidemias	
Methylmalonic acidemia	
Propionic acidemia	
Mucopolysaccharidosis	
Type 1 (Hurler syndrome)	
Type 2 (Hunter syndrome)	
Leukodystrophy/vascular disorders	
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	
Hereditary angiopathy with nephropathy, aneurysm and muscle cramps (HANAC)	
Unknown mechanism	
CNS phenotype of x-linked Charcot Marie Tooth disease (CMTX)	

immunoglobulins or plasma exchange.[14] However, there is no consensus to treatment of recurrences[14], in which a significant improvement is followed by a dramatic worsening of symptoms soon after completing a first course of immunotherapy – in our patient we chose to give a prolonged taper of oral prednisolone over six months, given the recurrence occurred after a clearly adequate (six weeks) course of oral steroid treatment.

Though she remains well in the past 4 years, there is concern that she remains at risk for an eventual MS diagnosis. The Canadian cohort followed from first ADS shows a moderate risk (28%) for progression to MS following an initial non-ADEM (i.e. mono- or polyfocal CIS) presentation.[7] Of 21 children with MS in Taiwan, 16 (76%) had CIS (polyfocal/brain in 13, monofocal (eye or spinal cord) in 3) had CIS and only 5 (24%) had ADEM, as a first ADS.[4]

Patient 2, with optic neuritis as a first sentinel event, went on to have an MS diagnosis after 3 months, as new asymptomatic brain lesions were

Table 2: Proposed MRI criteria for MS diagnosis in children

Criteria	KIDMUS criteria[16]	Callen criteria[17]	Verhey criteria[18]	2010 McDonald revision applied to a pediatric cohort[15]
Year published	2004	2009	2011	2012
Items	Either or both: 1. Corpus callosum long axis perpendicular lesion 2. Sole presence of well-defined lesions	At least 2 of: 1. ≥ 5 T2 lesions 2. ≥ 2 periventricular lesions 3. ≥ 1 brainstem lesion	Either: 1. One or more T1-weighted hypointense lesions OR 2. One or more periventricular lesions	*Dissemination in Space* ≥ 1 T2 lesions in at least 2 of 4 of the following areas: Periventricular, Juxtacortical, Infratentorial, or Spinal Cord. *Dissemination in Time* Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI
Sensitivity/Specificity	21% / 100%	85% / 98%	84% / 93%	100% / 89%
PPV/NPV	100% / 61%	97% / 90%	76% / 96%	71% / 100%

Abbreviations: PPV, Positive predictive value; NPV, Negative predictive value; KIDMUS, Kids with multiple sclerosis study group.

demonstrated on surveillance MRI. Risk of MS in children depends on the type of first ADS - low for ADEM (3%)[7] and transverse myelitis (13%)[15] and high for ON (36% of children by 2 years).[16] Mean time to MS diagnosis following a first ON in the Taiwan study was 7.2 months (range 1-48 months).[4] Our patient had asymptomatic brain lesions at first ADS – both "black holes" and T2-hyperintense white matter lesions (Figure 2A). MS risk is particularly high following isolated ON if asymptomatic T2-hyperintense white matter brain lesions are present (OR 28.0, $P < 0.001$, 95% CI, 6.3-125.1, adjusted for age).[17]

Making the diagnosis of MS in children is no different than in adults, and criteria for dissemination in time and space as defined in the 2010 revisions to the McDonald criteria have proven useful in children.[18,19] MRI criteria for MS in children have been proposed (Table 2)[20-22], and include the presence of a T1 hypointense lesion "black hole", which was seen in our patient at first presentation.[22]

Patient 2 had large cavitating lesions which may resemble tumefactive demyelinating lesions or Balo's concentric sclerosis. The majority of children with a tumefactive demyelinating brain lesion present with an ADEM illness, and have had a monophasic disease course.[23] Balo's concentric sclerosis is a variant of adult-onset MS with a rapidly progressive clinical course and is extremely rare in children.[24]

Up to 60% of children with multiple sclerosis have oligoclonal bands in the CSF.[7] Our patient tested negative, although it must be noted that this was done using protein electrophoresis, a less sensitive method as compared to isoelectric focusing.[25]

Interferon beta-1a is the most commonly used disease modifying agent in children with MS and is generally well tolerated with similar side effects to those seen in adults.[26] There is no consensus as to the choice of second line agents. Cyclophosphamide, effective in a series of MS children with refractory disease [27], was chosen in our patient due to cost concerns and familiarity of use in children with other rheumatologic disease. Rituximab, natalizumab and mitoxantrone are alternatives that have been safely used in children.[28,29]

Patient 3 has relapsing neuromyelitis optica, as evidenced by relapsing disease limited to the spinal cord and optic nerves.[30] The presence of a longitudinally extensive spinal cord lesion greater than 3 vertebral bodies in length, with or without anti-NMO Ig G (anti-aquaporin 4 antibody) positivity, completes the diagnosis.[31] Serological diagnosis for NMO was not available at the time of evaluation, but the clinical and radiological evidence in our patient met diagnostic criteria. Careful investigations for differential diagnosis as in Table 1, especially looking for other autoimmune disorders, was negative in this patient. In the only childhood series of NMO in children, those with a relapsing course are more likely to be positive for anti-NMO Ig G antibody than those with monophasic disease (78% with relapsing NMO vs 13% in monophasic NMO).[32] Azathioprine, mycophenolate mofetil and rituximab have proven to be safe and effective disease modifying therapies in children with relapsing NMO.[30]

CRION, a relapsing disease involving the optic nerves alone (patient 4) is seen in 3 - 9 % of patients who present with a first monofocal optic nerve CIS (optic neuritis).[33,34] Long term follow up is important in these patients, as relapsing disease may herald the onset of MS or Relapsing NMO. Again, the lack of asymptomatic brain or lesions in our patients may confer a favourable prognosis.[7,16,35]

In conclusion, early recognition of relapsing inflammatory demyelination in children is important as untreated disease results in repeated hospitalization and eventual disability. The spectrum of relapsing demyelinating syndromes, clinical presentation and neuroimaging findings in South East Asian children are generally similar to those observed in children in temperate world regions.

REFERENCES

1. Krupp LB, Tardieu M, Amato MP, *et al*. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013; 19:1261-7.
2. Fridinger S, Alper G. Defining encephalopathy in acute disseminated encephalomyelitis. *J Child Neurol* 2013.
3. Chong HT, Li PCK, Ong B, *et al*. Pediatric multiple sclerosis is similar to adult-onset form in Asia. *Neurology Asia* 2007; 12:37-40.
4. Weng WC, Yang CC, Yu TW, Shen YZ, Lee WT. Multiple sclerosis with childhood onset: report of 21 cases in Taiwan. *Pediatr Neurol* 2006; 35:327-34.
5. Visudtibhan A, Tuntiyathorn L, Vaewpanich J, *et al*. Acute disseminated encephalomyelitis: a 10-year cohort study in Thai children. *Eur J Paediatr Neurol* 2010; 14:513-8.
6. Thomas T, Ling S, D.W.S. C. First Acute Demyelinating Syndrome and Risk of Multiple

Sclerosis amongst Singapore children. (Abstract) Proceedings of the 12th International Child Neurology Congress. *Dev Med Child Neurol* 2012; 54:130-1.
7. Banwell B, Bar-Or A, Arnold DL, *et al*. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. *Lancet Neurol* 2011; 10:436-45.
8. Absoud M, Lim MJ, Chong WK, *et al*. Paediatric acquired demyelinating syndromes: incidence, clinical and magnetic resonance imaging features. *Mult Scler* 2013; 19:76-86.
9. Khor GL, Chee WS, Shariff ZM, *et al*. High prevalence of vitamin D insufficiency and its association with BMI-for-age among primary school children in Kuala Lumpur, Malaysia. *BMC Public Health* 2011; 11:95.
10. Peh SC, Nadarajah VS, Tai YC, Kim LH, Abdullah WA. Pattern of Epstein-Barr virus association in childhood non-Hodgkin's lymphoma: experience of university of malaya medical center. *Pathol Int* 2004; 54:151-7.
11. de-The G, Day NE, Geser A, *et al*. Sero-epidemiology of the Epstein-Barr virus: preliminary analysis of an international study - a review. *IARC Sci Publ* 1975:3-16.
12. Thomas T, Banwell B. Multiple sclerosis in children. *Semin Neurol* 2008; 28:69-83.
13. Krupp LB, Banwell B, Tenembaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007; 68:S7-12.
14. Dale RC. Acute disseminated encephalomyelitis. *Semin Pediatr Infect Dis* 2003; 14:90-5.
15. Thomas T, Branson HM, Verhey LH, *et al*. The Demographic, Clinical, and Magnetic Resonance Imaging (MRI) Features of Transverse Myelitis in Children. *J Child Neurol* 2012; 27:11-21.
16. Wilejto M, Shroff M, Buncic JR, Kennedy J, Goia C, Banwell B. The clinical features, MRI findings, and outcome of optic neuritis in children. *Neurology* 2006; 67:258-62.
17. Waldman AT, Stull LB, Galetta SL, Balcer LJ, Liu GT. Pediatric optic neuritis and risk of multiple sclerosis: meta-analysis of observational studies. *J AAPOS* 2011; 15:441-6.
18. Polman CH, Reingold SC, Banwell B, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69:292-302.
19. Sadaka Y, Verhey LH, Shroff MM, *et al*. 2010 McDonald criteria for diagnosing pediatric multiple sclerosis. *Ann Neurol* 2012; 72:211-23.
20. Mikaeloff Y, Adamsbaum C, Husson B, *et al*. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. *Brain* 2004; 127:1942-7.
21. Callen DJ, Shroff MM, Branson HM, *et al*. MRI in the diagnosis of pediatric multiple sclerosis. *Neurology* 2009; 72:961-7.
22. Verhey LH, Branson HM, Shroff MM, *et al*. MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. *Lancet Neurol* 2011; 10:1065-73.
23. Morin M-P, Patenaude Y, Sinsky AB, Banwell B, Sebire G. Solitary tumefactive demyelinating lesions in children. *J Child Neurol* 2011; 26:995-9.
24. Linnoila J, Chitnis T. Balo concentric sclerosis in children: A case series. *J Child Neurol* 2014.
25. Link H, Huang YM. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness. *J Neuroimmunol* 2006; 180:17-28.
26. Banwell B, Bar-Or A, Giovannoni G, Dale RC, Tardieu M. Therapies for multiple sclerosis: considerations in the pediatric patient. *Nat Rev Neurol* 2011; 7:109-22.
27. Makhani N, Gorman MP, Branson HM, Stazzone L, Banwell BL, Chitnis T. Cyclophosphamide therapy in pediatric multiple sclerosis. *Neurology* 2009; 72:2076-82.
28. Yeh EA, Waubant E, Krupp LB, *et al*. Multiple sclerosis therapies in pediatric patients with refractory multiple sclerosis. *Arch Neurol* 2011; 68:437-44.
29. Chitnis T, Tenembaum S, Banwell B, *et al*. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. *Mult Scler* 2012; 18:116-27.
30. Tillema JM, McKeon A. The Spectrum of Neuromyelitis Optica (NMO) in Childhood. *J Child Neurol* 2012; 27:1437-47.
31. Makhani N, Bigi S, Banwell B, Shroff M. Diagnosing neuromyelitis optica. *Neuroimaging Clin N Am* 2013; 23:279-91.
32. Banwell B, Tenembaum S, Lennon VA, *et al*. Neuromyelitis optica-IgG in childhood inflammatory demyelinating CNS disorders. *Neurology* 2008; 70:344-52.
33. Visudhiphan P, Chiemchanya S, Santadusit S. Optic neuritis in children: recurrence and subsequent development of multiple sclerosis. *Pediatr Neurol* 1995; 13:293-5.
34. Mizota A, Niimura M, Adachi-Usami E. Clinical characteristics of Japanese children with optic neuritis. *Pediatr Neurol* 2004; 31:42-5.
35. Absoud M, Cummins C, Desai N, *et al*. Childhood optic neuritis clinical features and outcome. *Arch Dis Child* 2011; 96:860-2.