

INFLAMMATORY AND AUTOIMMUNE DISORDERS OF THE NERVOUS SYSTEM IN CHILDREN

Russell C. Dale and Angela Vincent

10

OPSOCLONUS–MYOCLONUS SYNDROME

Michael R. Pranzatelli and Elizabeth D. Tate

Introduction

Opsoclonus–myoclonus syndrome (OMS) is a devastating disorder without a cure, and there is a paucity of neuropathology data, no radiological surrogate marker, and no animal model. Moreover, the rarity of OMS has frequently led to under-recognition and undertreatment, even by child neurologists, and this means that controlled therapeutic trials are not feasible.

The National Pediatric Myoclonus Center (NPMC) in the USA (www.omsusa.org) has managed patients with OMS for over 20 years, and the centre's database contains more than 300 children. This chapter summarizes recent developments and perspectives on paediatric OMS at our centre and elsewhere, and extends our previous reviews on the topic (Pranzatelli 1992, 1996, 2000a, 2005).

Epidemiology

The true incidence and prevalence of OMS are unknown. It is estimated that OMS occurs in about 2–4% of children with neuroblastoma, which is a higher frequency of paraneoplastic syndrome than in most cancers (Darnell and Posner 2006). However, occult neuroblastoma (Solomon and Chutorian 1968) has a very high rate of spontaneous regression (rare among human malignancies), so the estimate might be too high (Everson and Cole 1966, Nishihira et al 2000). According to the American Cancer Society, the annual occurrence of neuroblastoma in the USA is about 650 cases, predicting up to about 26 cases of OMS per year. In the database of the NPMC, tumour is detected in 45% of patients with OMS. Projecting from these figures, there should be approximately 58 new cases of OMS per year (26 cases presenting with tumour, 32 with no tumour found). However, it is quite likely that OMS is missed in its atypical forms and labelled as 'acute cerebellar ataxia'. These cases could number 40–50 per year, which would bring the total of annual new paediatric cases to 80–100 out of 83 million US children, or 0.12–0.1 per 100 000. As with neuroblastoma, OMS has a predilection for toddlers, and most cases are diagnosed before the age of 5 years (Tate et al 2005). There is a slight female preponderance (Bolthausen et al 1979, Talon and Stoll 1985). Despite the rare description of familial neuroblastoma, OMS has never been reported in more than one family member. There is an adult form of OMS, which appears to be aetiologically distinct.

Clinical features

Kinsbourne (1962) described the quintessential clinical features of OMS in a report of six cases – average age 12.5 months (range 6–18mo). Struck by the myoclonus, he called the disorder ‘myoclonic encephalopathy of infants’ and differentiated it from ataxia, specifically ‘acute cerebellar ataxia.’ Although he rejected the term ‘opsoclonus’ (opsoclonia), which had been coined by Orzechowski in the early 1900s, his description of the eye movements is consistent with opsoclonus.

The diagnosis of OMS is clinical. *Opsoclonus* is distinguished from *nystagmus* by its multidirectional, erratic, darting quality (for a review see Wong 2007). Myoclonus is a mixture of small- and larger-amplitude muscle jerks, giving rise to a tremulous appearance. It is primarily action induced, but in severe cases is present at rest. *Ataxia* in OMS begins as gait ataxia, with falling and poor coordination, and progresses to include titubation and loss of ambulation. In a study by the NPMC, parents were given a list of symptoms and asked to number them in order of appearance in their child. The results showed that ataxia was the earliest sign, explaining why the children are often misdiagnosed as having ‘acute cerebellar ataxia’ (Fig. 10.1).

In its typical presentation, OMS has no differential diagnosis (Fig. 10.1). The presence of opsoclonus should always prompt the diagnosis, having greater specificity than either myoclonus or ataxia. The prodrome is relatively similar both in tumour cases and in cases in which no tumour was found. Extreme irritability, sleeplessness, or rage in the presence of ataxia in a young child should suggest OMS. Acute cerebellar ataxia is not accompanied by opsoclonus or myoclonus and is regarded as a benign disorder of viral origin that requires no treatment. OMS must not, therefore, be misdiagnosed as acute cerebellar ataxia. Sadly, children with OMS have been sent home from the accident and emergency department, unable to walk or talk, with the parents being told that the problem is ‘viral,’ and ‘will go away on its own’.

In atypical cases (Fig. 10.1), a therapeutic challenge with adrenocorticotrophic hormone (ACTH) or steroids may help to make the diagnosis. In young infants with isolated opsoclonus, opsoclonus-like eye movement abnormalities, or mixed nystagmus and opsoclonus-like movements, the possibility of central nervous system infection, and ocular and intracranial lesions, as well as genetic disorders, should be considered. Often, no cause is found. Usually, more than one paraneoplastic disorder does not occur in a child with neuroblastoma, but vasoactive intestinal peptide-induced secretory diarrhoea may occur concurrently with OMS (Gesundheit et al 2004).

Although the dramatic neurological (motor) abnormalities of OMS first catch the eye, the neuropsychiatric manifestations contribute to acute and chronic problems. The profound sleep disturbance leaves the child highly irritable and given to rages, with aggressive behaviour and injurious or self-injurious biting. Children with the most severe course and multiple relapses may become cognitively impaired. In them, the IQ declines over a decade (more like dementia, unlike learning disability¹) but then stabilizes (unlike dementia). Other problems, such as attention-deficit disorder and persistent rage, are also frequent and aggravating but potentially treatable (Turkel et al 2006). Years of being in the ‘sick child’ role often leaves the child with OMS poorly socialized and a challenge to manage in school or at home.

1 North American usage: mental retardation.

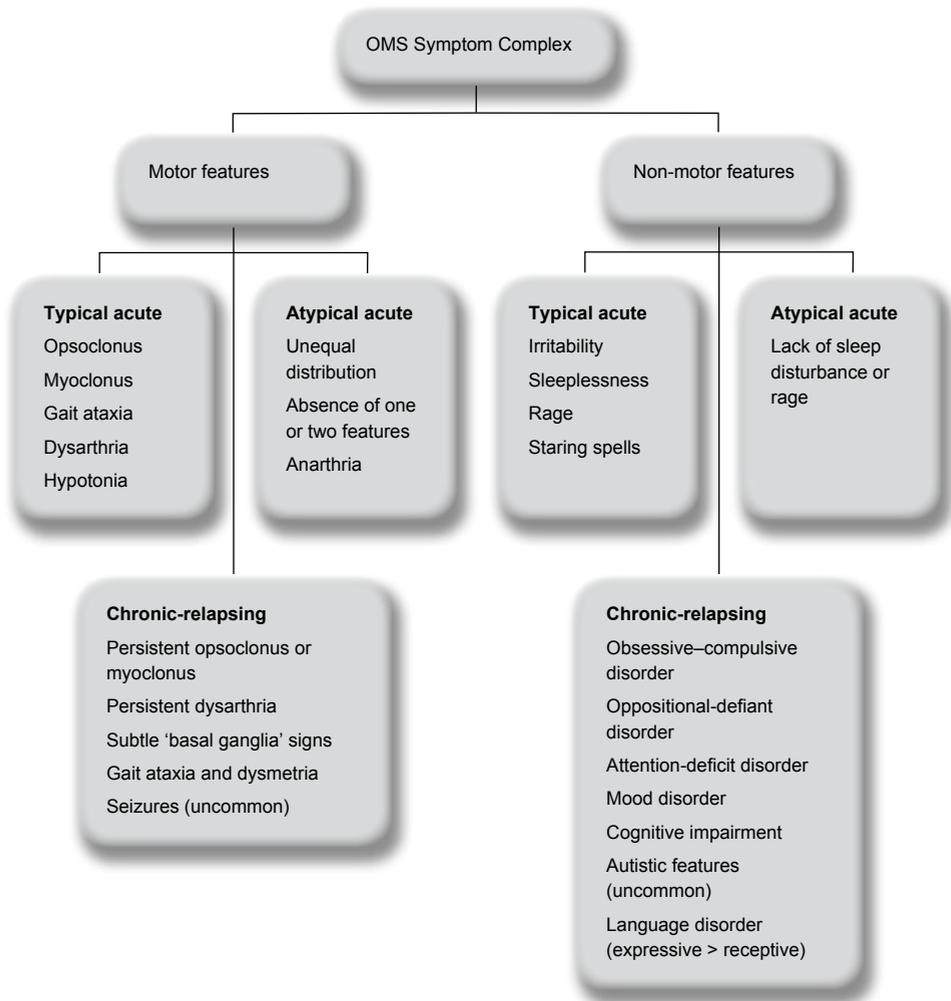


Fig. 10.1 Protean manifestations of opsoclonus–myoclonus syndrome (OMS). Beside typical OMS, there is also atypical presentation. The acute and chronic manifestations of OMS also differ. All of these features must be taken into account in devising a comprehensive treatment plan and arriving at a prognosis.

Investigation features

NEUROIMAGING

Most children are scanned by computed tomography (CT) or magnetic resonance imaging (MRI) when first evaluated, but the only brain abnormalities are incidental. No acute macropathology is revealed. There have been no long-term follow-up neuroimaging studies. In some cases, cerebellar atrophy is found (Hayward et al 2001), especially of the cerebellar vermis (Pranzatelli et al 2002a), but most children do not display cerebellar abnormalities on

routine MRI or MR spectroscopy. Newer approaches, such as voxel-based morphometry and positron emission tomography, may be more informative (Table 10.1).

TUMOUR IMAGING

The most reliable method for diagnosing a neuroblastoma is not to rely on one type of scan. High-resolution CT of chest, abdomen, and pelvis, carried out with oral contrast, probably has the highest yield. In infants, especially with a Horner syndrome, the neck should be scanned as well. The tumour can be minute. If the CT is negative, we would recommend a ¹³¹I-meta-iodobenzylguanidine (MIBG) scan (Boubaker et al 2003). The ¹³¹I-MIBG scan is sensitive for neuroblastoma, but can give false-positive and -negative results (McGarvey et al 2006). ¹¹¹In-pentetreotide scanning is another option (Shalaby-Rana et al 1997), but the bright adrenal signal obscures any underlying suprarenal neuroblastoma. Because neuroblastoma may not be found until later in the course of OMS, we routinely do body cavity MRI every 6 months for 2 years after OMS presentation. If the child is doing poorly, we would choose CT over MRI for that purpose.

BODY FLUID AND TUMOUR TESTING

Cerebrospinal fluid (CSF) pleocytosis and oligoclonal bands are present in some, but not most, children with OMS. Pleocytosis may be more common early in the course or with a relapse.

TABLE 10.1
Summary of neuroimaging reports in paediatric opsoclonus–myoclonus syndrome

Scan	Description	Finding	Reference
MRI	7 children with neuroblastoma	Cerebellar atrophy	Hayward et al 2001
	1 adult, 41y after OMS onset – had severe onset	Cerebellar vermis atrophy	Pranzatelli et al 2002a
	8 children with OMS, 7 siblings	Normal	Blüml et al 2006
MRS	14 children, 64 total spectra in nine brain regions	Normal MR spectra, including cerebellar vermis	Kuhn et al 2002
	8 children with OMS, 7 healthy siblings, 3 brain regions	Normal MR spectra in all patients. Significant relation between NAA/Cr ratio in cerebellar hemisphere and IQ in OMS	Blüml et al 2006
VBM	8 children with OMS, 7 healthy siblings	Decreased vermis volume only	Blüml et al 2006
SPECT	2 children	1 patient had cerebellar hyperperfusion, the other had hypoperfusion	Oguro et al 1997

Cr, creatine; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetyl aspartate; OMS, opsoclonus–myoclonus syndrome; SPECT, single photon emission computed tomography; VBM, voxel-based morphometry.

The concentration of CSF immunoglobulins is usually not increased (Pranzatelli et al 2006). In blood, elevated neuron-specific enolase or ferritin raises suspicion of a tumour. Testing for urinary catecholamines, such as homovanillic acid and vanillylmandelic acid, can be positive, but a negative test does not rule out neuroblastoma.

INFECTIOUS AGENTS

It was noted previously that multiple infectious agents have been associated with paediatric OMS (for a review see Pranzatelli 1992). These case reports include new putative associations with *Mycoplasma pneumoniae* (Chemli et al 2007), enterovirus 71 (McMinn et al 2001), group A streptococcal infection (Jones et al 2007), Epstein–Barr virus infection (Cardesa-Salzmann et al 2006), and HIV infection after initiation of antiretroviral therapy (fatal disseminated cytomegalovirus infection – van Toorn et al 2005).

The problem with attributing OMS to microbial agents alone is best illustrated by a child with microbiologically documented acute Epstein–Barr viral infection at OMS presentation and an occult thoracic ganglioneuroblastoma diagnosed 5 months later (Cardesa-Salzmann et al 2006). Although OMS is rare, childhood infections are common. Similarly, CSF pleocytosis does not rule out the presence of neuroblastoma (Bolthausen et al 1979). Nevertheless, there is a need for systematic antimicrobial screening in OMS.

Immunopathology (Fig. 10.2)

AUTOANTIBODIES

OMS is an autoimmune disease. Although autoantibodies have been described in a number of other adult paraneoplastic disorders, these disorders are usually not autoantibody mediated (the autoantibodies are markers rather than being pathogenic) (for a review see Honorat and Antoine 2007). ‘Onconeural antigens’ – shared by brain and tumour – provoke a ‘friendly fire’ attack of the immune system on the brain (Pranzatelli 2000b), probably through molecular mimicry. In paediatric OMS, several different autoantibodies have been found in research laboratories (Table 10.2) but to apparently different antigens (Manley et al 1995, Connolly et al 1997, Antunes et al 2000). In contrast, commercial screening for ‘paraneoplastic autoantibodies’ is overwhelmingly negative and not cost-effective (Pranzatelli et al 2002b). Newer techniques for autoantibody detection, such as serological analysis of recombinant cDNA expression libraries (Bataller et al 2003) and flow cytometry (Blaes et al 2005, Korfei et al 2005, Kirsten et al 2007), have detected other evidence of putative autoantibodies. Antineuronal antibodies do not correlate with long-term outcome or treatment for OMS (Rudnick et al 2001). Autoantibody findings are reviewed in Table 10.2.

In children without demonstrable tumours, various autoantibodies also have been reported. In two females, aged 10 and 16 years, serum and CSF antibodies against neuroleukin, a 56-kDa protein, were detected in the setting of poststreptococcal pharyngitis (Candler et al 2006). This age range is well outside the norm for neuroblastoma and typical OMS, as <10% of neuroblastomas occur over the age of 10 years. Additional studies are needed.

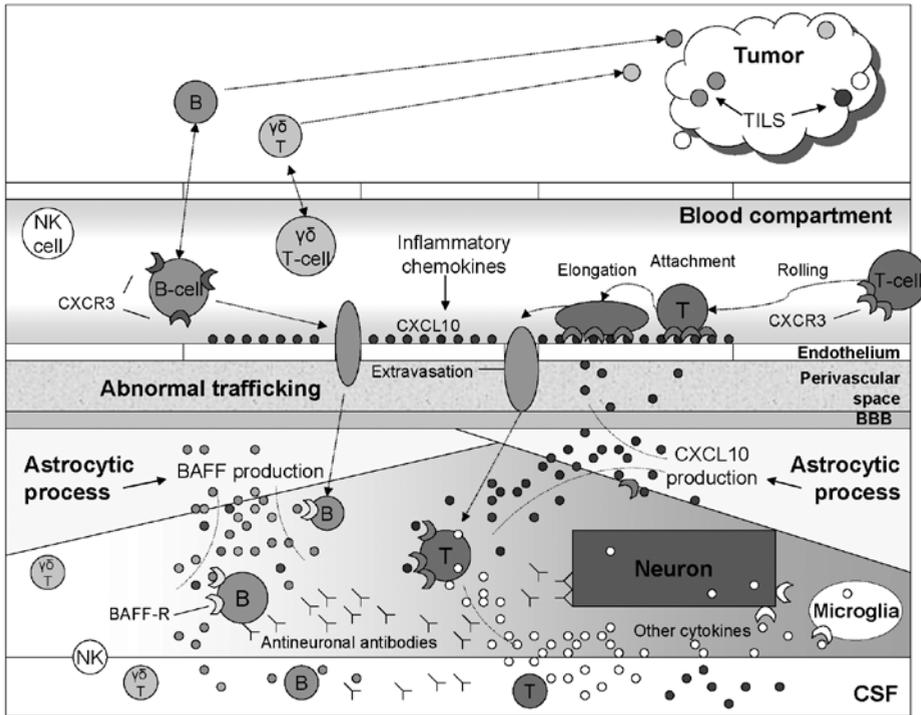


Fig. 10.2 Lymphocyte trafficking, cytokines, and autoantibodies in OMS. Types of lymphocytes that infiltrate neuroblastomas are also those that traffic into the central nervous system (CNS), where their frequency may be abnormal because of immune dysregulation. There is recent evidence that inflammatory chemokines, such as CXCL10, are produced by reactive astrocytes and recruit lymphocytes into the brain. Perivascular astrocytic processes (end-feet) and the glia limitans form the blood–brain barrier. Astrocytes are also involved in brain homeostasis and maintaining neuronal function. Inflammatory chemokines, displayed on endothelial cells, attract lymphocytes that express receptors for the chemokines. CXCR3 is the receptor for CXCL10. The lymphocytes follow the chemokine gradient into the CNS. Cytokines, such as B-cell activating factor (BAFF), can create an environment within the brain that sustains the infiltrating B cells and T cells. BAFF-R is a BAFF receptor expressed by B cells. B cells produce antineuronal autoantibodies. Activated microglia, which can also secrete chemokines, and dendritic cells (not shown) may also play a role. TIL, tumour-infiltrating lymphocyte. A colour version of this figure is available in the colour plate section.

CELLULAR IMMUNE ABNORMALITIES

Most human autoimmune diseases also manifest cellular immune abnormalities (Davidson and Diamond 2001). Such is the case for OMS. Although there is usually no CSF pleocytosis in OMS, the cells demonstrate a phenotypic expansion. CSF studies revealed an expansion of B cells, cytotoxic/suppressor T cells, and gamma/delta T cells (Pranzatelli et al 2004b). Under ‘resting’ conditions, the frequency of different lymphocyte subsets in the brain remains tightly controlled (Hickey 1999). For example, the percentage of CSF B cells in healthy children is

TABLE 10.2
Putative autoantibodies in paediatric opsoclonus–myoclonus syndrome

Antibody	Finding	Reference
Antineurofilament	Immunocytochemistry in nine children revealed IgM and IgG binding to cerebellar Purkinje cell cytoplasm and some axons; western blot showed binding to several neural proteins, including 210kDa neurofilament	Connolly et al (1997)
	No antineurofilament antibodies found in 16 sera by western blot	Antunes et al (2000)
Anticerebellar granule cell	10 of 14 cases had autoantibodies to surface of isolated rat cerebellar granular neurons to the same, but unidentified, autoantigen; found by flow cytometry after removal of blocking antibodies	Blaes et al (2005)
	Indirect immunofluorescence and western blot revealed IgG binding to intracellular autoantigens in 11 patients with opsoclonus–myoclonus syndrome (OMS) and one comparison individual – caused inhibition of cell proliferation and induced apoptosis in neuroblastoma cell line	Korfei et al (2005)
	Both intracellular and surface binding antibodies in OMS belonged mainly to IgG3 subclass, although total serum IgG3 level was normal	Beck et al (2007)
Anti-Hu/ antineuronal (unspecified)	Screening of sera by western blot and immunocytochemistry found 13 out of 16 patients with OMS (81%) and 11 of 48 comparison individuals (25%) positive for antineuronal IgG; IgM antineuronal antibodies were present in 19% of OMS and 13% of comparison individuals; no antibodies against neuroblastoma except anti-Hu in four patients with paraneoplastic OMS	Antunes et al (2000)
	Commercial screening for anti-Hu (also anti-Ri and anti-Yo) was negative in 59 sequential cases	Pranzatelli et al (2002b)
Anti-brainstem	Screening of 21 sera (adult- and paediatric-onset OMS) by SEREX in a brainstem cDNA library; multiple antibodies found, none in all opsoclonus–myoclonus syndromes, two postsynaptic densities, neuronal expression proteins (RNA- or DNA- binding and zinc-finger proteins), and diverse unidentified proteins	Bataller et al (2003)

<1% (Pranzatelli 2004b). However, in OMS both the autoreactive CD5⁺ B-cell subset (T cell independent) and CD5⁻ B cells (T cell dependent) are expanded in the CSF (Pranzatelli et al 2005d). Also, the CSF ratio of helper/inducer T cells (Th) to cytotoxic/suppressor T cells is reduced, indicating immune imbalance. The only abnormality commonly found in peripheral blood is a low helper–suppressor T-cell ratio (Pranzatelli et al 2004c).

The percentage of CSF B cells and gamma/delta T cells correlates positively with severity, whereas the percentage of Th cells is negatively correlated. The frequency of CSF B cells varies with OMS duration: the highest B-cell percentages were found in acute cases.

Children with chronic relapsing OMS have less abnormal CSF B-cell expansion. The finding of increased CSF neopterin levels in OMS also supports cellular immune abnormalities, but the neopterin concentration was not a useful biomarker (Pranzatelli et al 2004a).

Cytokines

Chemokines, short for chemoattractant cytokines, recruit lymphocytes into areas of inflammation. Recently, CSF levels of the inflammatory Th1 chemokine CXCL10 (formerly IP-10) were found to be elevated in untreated OMS (Pranzatelli et al 2007) (Fig. 10.2). CXCL10 is a sentinel molecule that initiates neuroinflammation, recruiting both T cells and B cells. Serum CXCL10 levels were normal, indicating intrathecal secretion. In multiple sclerosis, increased CSF CXCL10 is produced by reactive astrocytes (Sørensen et al 1999). By analogy, elevated levels of CSF CXCL10 may be the first evidence of astrogliosis in OMS. Transformation of resting into reactive astrocytes, which can result in a glial scar, is regulated by cytokines in brain parenchyma. B-cell activating factor (BAFF), a cytokine of the tumour necrosis factor family, is also produced by astrocytes (Krumholz et al 2005) and is upregulated in OMS (Pranzatelli et al 2008a). It fosters B-cell survival and antibody production, both factors in OMS. ACTH and steroids (not IVIg) decrease serum and CSF BAFF (Pranzatelli et al 2008), which correlates with CSF autoantibodies in OMS (Fühlber et al 2009). These newly described central properties of ACTH join the list of ACTH effects on neural plasticity, neurotransmission, and neurometabolism (for a review see Pranzatelli 1994, Wikberg et al 2000).

Tumours

Neuroblastomas are infiltrated with lymphocytes to an extent not found in other solid tumours, and are particularly infiltrated with lymphocytes in children with OMS (Martin and Beckwith 1968, Cooper et al 2001). The majority are non-aggressive, low-stage tumours (i.e. stage 1 out of 4, as defined by the International Neuroblastoma Staging System). They lack *N-myc* amplification (Gambini et al 2003). Tumour types include neuroblastoma, ganglioneuroblastoma, and ganglioneuroma, in order of increasing neural differentiation. Neuroblastoma arises from any neural crest constituent of the sympathetic nervous system. The tumours stain positive for neuron-specific enolase, glial fibrillary acidic protein, neurofilament, and many other shared onconeural proteins. They produce neurochemicals and receptors, and can even be differentiated by the type of serotonin receptor they express (Pranzatelli and Balletti 1992).

NEUROPATHOLOGICAL STUDIES

Post-mortem and brain biopsy cases are scant, because neither the tumour nor OMS is lethal. Most of the limited information available pre-dates modern immunostaining approaches, and the children had lesions that are seldom found in OMS (Table 10.3). For these reasons, it is difficult to interpret these studies. However, the cerebellum, usually the vermis, was the only brain area found to be abnormal, and astrocytic gliosis was common to all the lesions.

ALTERED NEUROCHEMISTRY

Although the clinical features of OMS would suggest abnormalities of neurotransmission, the exact neurotransmitter system involved is unclear. The CSF dopamine metabolite

TABLE 10.3
Summary of autopsy and brain biopsy cases of paediatric opsoclonus–myoclonus syndrome

Type	Description	Finding	Reference
Autopsy	6 y.o. with metastatic ganglioneuroblastoma, treated with chemotherapy	Mild patchy loss of Purkinje cells, increase in astrocytes with abnormal forms (gliosis), and foci of fat-laden cells (demyelination)	Ziter et al (1979)
	3 y.o. with cerebellar subcortical lesion (vermis and hemisphere) on MRI and ganglioneuroblastoma-associated Cushing syndrome	Confirmed cerebellar lesions and regenerative gliosis; reactive cells positive for monocyte–macrophage antigens; no T- or B-cell infiltrates	Clerico et al (1993)
Biopsy	3 y.o. with 2-y history of severe opsoclonus–myoclonus syndrome	Normal frontal cortex	Kinsbourne (1962)
	3 y.o. with cerebellar vermis lesion on imaging studies, low attenuation on computed tomography, high signal intensity on magnetic resonance imaging; no neuroblastoma found	Marked Purkinje and granule cell loss with striking astrocytic gliosis	Tuchman et al (1989)

homovanillic acid was 38% lower in 27 children with OMS than in age- and sex-matched comparison individuals, and the CSF level of serotonin metabolite 5-hydroxyindoleacetic acid was also 29% lower (Pranzatelli et al 1998a). However, manipulation of monoamine metabolism is not clinically beneficial in OMS (for a review see Pranzatelli 1992). Free CSF choline was normal in 30 cases of OMS (Pranzatelli et al 1998b). Although anecdotal responses to high-dose clonazepam or gabapentin have been used to propose a GABAergic hypothesis of opsoclonus (Bartoš 2006), there are no supportive laboratory data in humans. We found that CSF free amino acid concentrations in OMS are normal (Pranzatelli et al 2008b). Sedatives, including antihistamines, chloral hydrate, opiates, and certain anaesthetics, such as ketamine, can trigger paradoxical responses in OMS, whereas propofol does not (Tate et al 1994).

NEUROANATOMICAL LOCALIZATION

The cerebellum contributes to higher functions during development and plays a role in primitive emotions (Riva and Giorgi 2000) and early language development (Lieberman 2002). ‘Cerebellar mutism’ may follow posterior fossa lesions and surgery in children (Koh et al 1997). In adults, cerebellar cognitive–affective syndrome (Schmahmann and Sherman 1998), psychiatric symptoms (Hamilton et al 1983), and involvement in complex human behaviour (Botez et al 1989) have been described. In animals, the cerebellum is implicated in learning (Marr 1969, Lalonde and Botez 1990). Cerebellar gait ataxia results from anterior vermis lesions, truncal titubation from posterior vermis lesions, and appendicular dysmetria from dysfunction of cerebellar hemispheres. Opsoclonus and myoclonus are seldom attributed to the cerebellum (Wertenbaker et al 1981, Mink et al 2003).

Although cerebellar involvement seems likely and is accepted regarding OMS, brainstem involvement has also been proposed, initially by Kinsbourne (1962). The brainstem is involved in generation of saccadic eye movements (Fuchs et al 1985) – opsoclonus is ‘saccadomania’ – through the interplay of burst cells and omnipause neurons (midline pontine neurons that control some oculomotor behaviour). Myoclonus also can be evoked by brainstem mechanisms (for a review see Pranzatelli 1992). In experimental animals, microinjection of certain pharmacological agents within deep medullary nuclei (nucleus gigantocellularis reticularis) evokes myoclonus. In rapid eye movement sleep, the source of myoclonic paradoxical excitation is the brainstem reticular formation. The cerebellum and the brainstem influence each other in many ways, and perhaps breakdown of the interaction is important in OMS.

Another issue is how to conceptually integrate the comorbid features of OMS, such as attention-deficit disorder (the majority of cases), obsessive–compulsive disorder (not uncommon), and seizures (uncommon). These disorders have been modelled on frontal–subcortical structures and circuitry, with special emphasis on the prefrontal cortex and its connections to the striatum and cerebellum (Arnsten 2006).

Treatment and management

DISEASE-MODIFYING IMMUNOTHERAPY

The tenets of immunotherapy for OMS should be (1) to start treatment as soon after onset as possible, (2) to gain a full neurological remission, and (3) to prevent relapse. Although they may sound simple, these goals can be a challenge. The clinician does have some control over when treatment is started. It is extremely important not to wait for an improvement from tumour resection alone, as it is usually insufficient and only occurs in about one-third of the cases (Tate et al 2005). To gain a full neurological remission, the best approach is to treat fully at the front end rather than use the ‘add-one-at-a-time’ approach. The clinician should be aware that an initial blush of response to conventional agents belies the gravity of OMS, and relapses are common. Zero tolerance is the rule: if the response is inadequate, modify the approach.

Data from the National Pediatric Myoclonus Center suggest that early treatment gives the patient the best chance of remission without permanent residual deficits. There has been a lack of truly early treatment – within hours or a few days of onset. A 13-year survey in the USA revealed that the average delay to diagnosis was 11 weeks, with another 6-week delay until the initiation of therapy (Tate et al 2005).

Preventing relapse is not always possible, but the clinician should avoid abruptly stopping treatments or engaging in rapid tapering (yo-yo effect), and avoiding reduction of immunotherapy over winter months in cold weather areas. The parents should be encouraged to take reasonable precautions to protect against infections, the second major cause of relapse. Ultimately, the immune system must learn tolerance to the instigating antigen/antigens in OMS, and that requires time (usually a few years) and eradication of ongoing inflammation.

Choice of agents

The treatment of OMS is far from standard and often depends on whether the child is seen first by a neurologist or an oncologist, and whether (or not) a tumour is found. Conventional

options are steroids (prednisolone or dexamethasone), ACTH, and IVIg. Most neurologists are more familiar with the short-term use of ACTH for infantile spasms, but the pathophysiology of OMS is vastly different (Pranzatelli 2005) and the ACTH treatment protocol is much longer. The availability and preference for porcine ACTH₁₋₃₉ versus synthetic ACTH₁₋₂₄ varies globally. Development of serum anti-ACTH antibodies is uncommon (Pranzatelli et al 1993).

Corticosteroids have been used in myriad forms for years to treat OMS (for a review see Pranzatelli 1992). There have been no dose-equivalent steroid trials, so efficacy of one form over another remains to be established. More recently, dexamethasone has been revived and used in pulses of 20mg/m² per day over 3–5 days monthly (Ertle et al 2008). It also has been combined with cyclophosphamide in chronic relapsing OMS (Wilken et al 2007). Response to IVIg was initially reported in a few cases of OMS (Sugie et al 1992, Petruzzi and DeAlarcon 1995, Veneselli et al 1998), and is now recognized as a valid indication for IVIg (Feasby et al 2007). Acute rather than long-term benefit has been noted (Mitchell 2002). Cyclophosphamide use is anecdotal, reported to benefit (Wilken et al 2007) or worsen OMS (Mitchell et al 2002). The Children's Oncology Group is conducting a trial of cyclophosphamide and prednisone, with IVIg as a treatment arm. Rituximab (a monoclonal anti-CD20 antibody) in OMS cases with neuroblastoma reduced OMS severity score to 48% of pretreatment values after completion of 4 weeks of treatment (Tersak et al 2005). There are currently two phase 1/2 rituximab clinical trials in progress in the USA. Table 10.4 reviews the historical progress of OMS treatment, and current pending treatment trials.

Plasma exchange has no proven role in OMS, but there have been a few enthusiastic case reports (Yiu et al 2001, Armstrong et al 2005). Immunoabsorption, the removal of additional IgG by attaching a staphylococcus A protein column, was reported as useful in adult-onset cases, but the columns are no longer being manufactured. Leucocytapheresis has not been explored. Apheresis can result in cellular immunomodulation, but the effect may be transient (Smith 1997).

Development of adjunctive and front-end combination therapies

The NPMC has developed many treatment protocols for OMS (Table 10.4). Kinsbourne's initial descriptions (1962) suggested that ACTH was better at inducing a neurological remission than oral steroids. The initial response of most patients was marvellous, but the relapse rate was high and there were treatment failures. To increase the response rate and decrease relapse, combination therapies were devised (Table 10.4). The best ratio of benefit to side-effects was produced by 2g/kg IVIg at induction. To allow steroid sparing, azathioprine was used (triple therapy) (Pranzatelli 1996, 2000). Cyclophosphamide was trialled as an alternative steroid-sparing agent instead of azathioprine. By the end of that decade, it was clear that combination therapy was more beneficial, but that better agents were still required (Table 10.4).

The finding of B-cell expansion in the CSF made therapy less empiric. Rituximab (a B-cell depletion therapy) used in adjunction to ACTH and IVIg induced remission (Pranzatelli et al 2003, 2005d, 2006) (Table 10.4).

We have also evaluated the effect of conventional immunotherapy and chemotherapy on the cellular biomarkers. Rituximab often reduced the CSF B-cell percentage to

TABLE 10.4
Opsoclonus–myoclonus syndrome clinical trials and case series
of the National Pediatric Myoclonus Center

Start year	Agent	<i>n</i>	Description	Results	Reference
<i>Symptomatic treatments</i>					
1988	L-5-hydroxytryptophan + carbidopa	5	Randomized, double blinded, crossover, placebo controlled ^{a,b}	No benefit	Pranzatelli et al (2002)
1991	Piracetam	5	Randomized, double blinded, crossover, placebo controlled ^a	No benefit	Pranzatelli et al (2001)
1993	Naltrexone	5	Randomized, double blinded, crossover, placebo controlled	No benefit	Pending
2001	Trazodone	19	Open label	Improved sleep and rage	Pranzatelli et al (2006)
2001	Risperidone	30	Open label	Improved rage	Pending
<i>Disease-modifying treatments</i>					
1987	ACTH (Acthar gel)	8	Open label ^{a,b}	50–70% improvement	Pranzatelli et al (1998a)
1992	ACTH+IVIg	24	Open label ^a	Synergistic	Pending
1993	Azathioprine	5	Open label, adjunctive ^a	Steroid sparer	Pranzatelli et al (1996)
1994	IVIg dose–response	25	Open label ^a	1–2g/kg best side-effect profile; 40% response rate	Pending
1995	Cyclophosphamide	13	Open label, adjunctive ^{a,c,d}	Anti-B-cell effects in CSF	Pranzatelli et al (2005c)
2001	Mycophenolate mofetil	13	Open label, adjunctive ^{a,c,d}	Reduced T-cell activation, but not relapse	Pranzatelli et al (2009)
2001	Rituximab	16	Open label, 6mo, adjunctive ^{a,c,d}	44% reduction in group severity; profound anti-B-cell effects in CSF	Pranzatelli et al (2006)
2003	Rituximab + chemotherapy	22	Open label, adjunctive ^{a,c,d}	Compatible	Pending
2004	Plasma exchange + immunoadsorption	4	Open label, adjunctive ^{a,c,d}	Pending	Pending

TABLE 10.4
Continued

Start year	Agent	n	Description	Results	Reference
2005	FLAIR (front-loaded ACTH, IVIg, rituximab)	25	Time course and pharmacokinetic study, ly, front-end triple therapy vs adjunctive ^{a,c,d}	Unique pharmacokinetic data; clinical efficacy in 3–4wks in either study arm	Tate et al (2007)
2005	Dual chemotherapy	7	Open label, adjunctive ^{a,c,d}	Pending	Pending
2005	Triple chemotherapy	11	Open label, adjunctive ^{a,c,d}	Pending	Pending
2006	Rituximab + rituximab	SE	Repeated cycle at 6–12mo, open label, adjunctive ^{a,c,d}	Pending	Pending
2007	Rituximab	25	Mechanistic study ^{a,c,d}	Pending	Pending
2007	Rituximab + pulse dexamethasone + IVIg	SE	Open label, front end ^{a,c,d}	Pending	Pending

^aAdjunctive treatments were added to ACTH + IVIg.

^cChemotherapy included 6-mercaptopurine, methotrexate, or cyclophosphamide.

^a Used opsoclonus–myoclonus syndrome evaluation video scale, scored by a blinded, trained observer.

^b Correlation with CSF neurochemicals.

^c Correlation with CSF immunophenotype.

^d Comparison with immunological comparison individuals.

ACTH, adrenocorticotrophic hormone; CSF, cerebrospinal fluid; IVIg, intravenous immunoglobulin; SE, still enrolling.

zero, and the effect was usually long-lasting and associated with significant clinical benefit. At standard doses, ACTH, steroids, and IVIg usually do not alter CSF lymphocyte subset frequencies (Pranzatelli et al 2004b). Mycophenolate mofetil reduced CSF T-cell activation, but not B-cell expansion (Pranzatelli et al 2009), and cyclophosphamide reduced the percentage of CSF B cells, although not as efficiently or completely as rituximab (Pranzatelli et al 2005c).

At present we use a panel of CSF protein biomarkers, including chemokines and other cytokines, as part of the evaluation of OMS in order to improve and rationalize immunotherapy. Table 10.4 summarizes the current treatment protocols used at NPMC, and details of a CSF biomarker approach to direct therapy are shown in Figure 10.3. The optimal protocol has yet to be defined.

Tumour therapy

Treatment for OMS should not be based on whether or not a tumour is found, unless the tumour is at a high stage. Most oncologists would then use multi-agent chemotherapy. However, high-stage tumours in OMS are uncommon, so there are no data to determine if aggressive

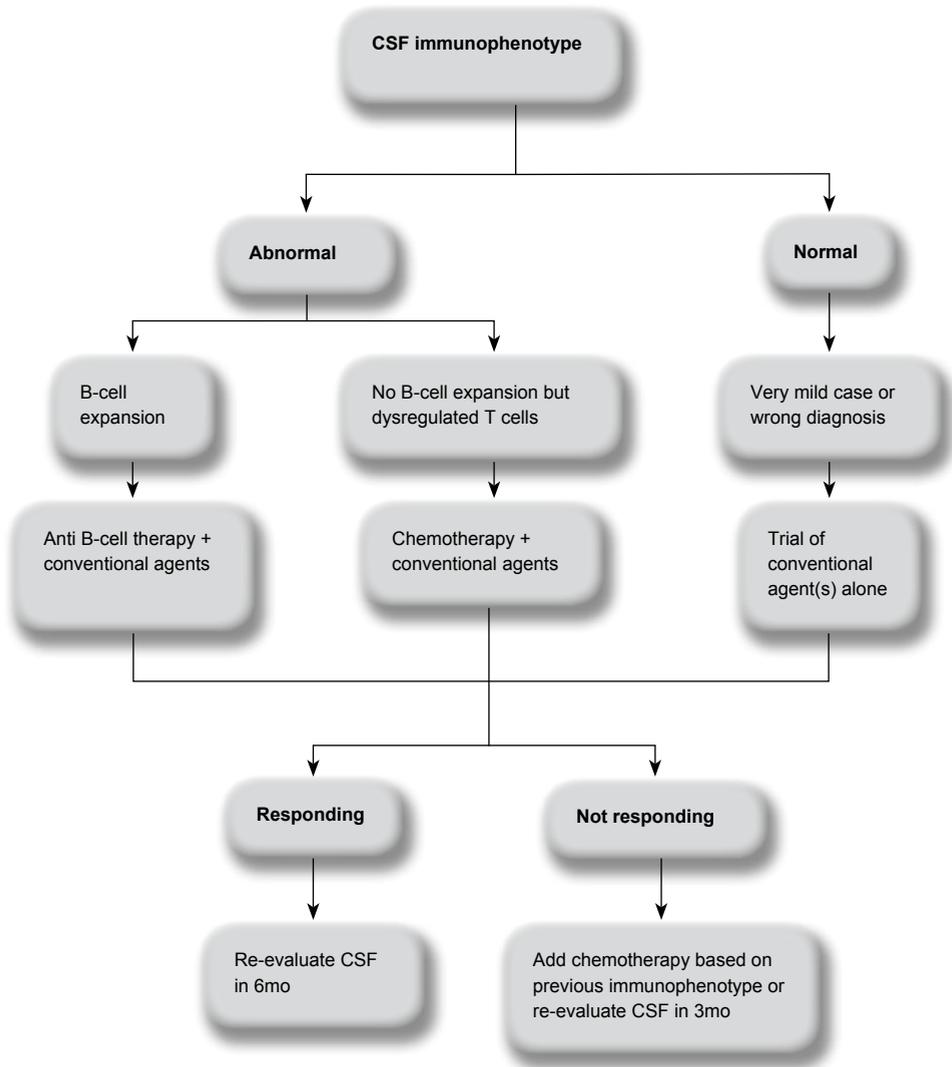


Fig. 10.3 Cerebrospinal fluid (CSF) biomarker-based treatment algorithm currently being developed by Pranzatelli. CSF biomarkers can be used to direct therapy and individualize treatment, while learning more about the immunopathology of opsoclonus–myoclonus syndrome (OMS). Children with B-cell expansion should not be treated with conventional agents alone, because the agents lack anti-B cytotoxic properties. T-cell dysregulation indicates that the immune system has not learned tolerance to OMS antigens and relapse is still possible.

antitumour therapy is justified, given the tendency of neuroblastoma in OMS to follow a more benign course. The uncharacteristically favourable prognosis for tumour survival in OMS has been known for more than 30 years (Altmann and Baehner 1976).

Symptomatic treatment

Thus far, the discussion has focused on disease-modifying immunotherapy. Children with OMS often also need temporary symptomatic therapies for sleep, rage, and attention-deficit disorder/attention-deficit–hyperactivity disorder. Their families also need relief from these very disruptive, relationship-testing problems.

Sleep disturbances, such as prolonged sleep latency, fragmented sleep, reduced quantity of sleep, snoring, and non-restorative sleep, were reported by parents of 32 out of 51 children with OMS (Pranzatelli et al 2005a). Rage was more common in children sleeping <10 hours per night. Nineteen of those with the most disruptive sleep pattern were treated with trazodone, a soporific serotonergic agent. Administration of trazodone at bedtime improved sleep and rage in 95% of the children and was well tolerated, even in toddlers.

When trazodone alone provides insufficient improvement of rage, risperidone is a good option. Beginning at the lowest dosage, the dose can be titrated for rage control if necessary. Other atypical antipsychotic agents can be used instead. However, rage that is unresponsive to immunotherapy or symptomatic therapy should always suggest active autoimmune disease.

There have not been any comparative studies of drugs for attention-deficit disorder/attention-deficit–hyperactivity disorder in OMS, although it is a very common problem, affecting at least one-third of cases (Tate et al 2005). Non-stimulant and stimulant agents have been used. Children with chronic OMS and rage may exhibit more aggressive behaviour on stimulants. The co-occurrence of cognitive impairment in OMS limits responsiveness to drugs for attention-deficit disorder/attention-deficit–hyperactivity disorder.

Non-pharmacological therapies

Children with moderate or severe OMS should be regarded as ‘high risk’ developmentally, and their parents need to be appropriately counselled upfront. They benefit from early intervention programmes with speech and occupational therapy. Because dysarthria and expressive language are so problematic, long-term speech therapy is usually required. Socialization with peers can help stimulate language development. Because of the extremely high divorce rate among parents of children with OMS, parents should be advised that OMS affects the whole family, and they should seek counselling early in the course. The healthy siblings, who bear the brunt of OMS rage and aggression, should be included. It is also important to paint a clear picture of the risk–benefit ratio of immunotherapy when used by experienced health-care providers. Families usually have more to fear from the symptoms of OMS than they do from the treatments.

Prognosis and outcome

It appears that the prognosis of OMS depends chiefly on neurological severity at onset, the onset age, how long the child remained untreated, whether a full neurological remission was ever achieved, and the number of relapses. Loss of ability to walk or speak at onset, infant onset, incomplete response to treatment, and multiple relapses carry the worst prognosis. Given the critical periods for neural and immune system development, these risk factors can be understood. Presence or absence of a tumour seems to matter little to the course of OMS, but this probably cannot be factored independently given the number of other variables. The

largest study was a 13-year survey of 105 children with OMS treated primarily with conventional (steroid) immunotherapy (Tate et al 2005). Forty-one per cent were positive for neuroblastoma. Tumour resection alone did not provide adequate therapy for most; response was evenly divided among the designations of 'better', 'worse', or 'unchanged'. Immunotherapy was often delayed for months by waiting to see the outcome of surgical resection. ACTH, prednisone, and IVIg were used with equal frequency, but ACTH was associated with the best early response. More than half of the children had relapses. Residual behavioural, language, and cognitive problems occurred in the majority. More than 80% of patients had behavioural problems, expressive language dysfunction, and ataxia; 69% had OCD. Of school-aged children, 28% were mainstreamed, 42% were in special education, and 33% were in combined programmes. Twenty-six per cent had been held back a grade. More than 90% were receiving speech, occupational, or physical therapies. The authors concluded that such a delay in diagnosis and treatment of OMS is unacceptably long. An earlier study of 54 patients also noted more rapid response to ACTH than to steroids but significant long-term neurological morbidity (Pohl et al. 1996).

Other information about long-term outcome comes from small case series. Relapsing OMS is dominated by cognitive and behavioural problems (Klein et al 2007). In 11 other cases (73% neuroblastoma), eight sustained severe developmental disability, and neither prednisone nor tumour resection was effective (Hammer et al 1995). This report intimated that presence of tumour carried a worse neurological prognosis. In a questionnaire study of 21 children with OMS and neuroblastoma, 74% had developmental or neurological sequelae (Rudnick et al 2001). Lower tumour stage correlated with late sequelae. In another study in 17 patients with OMS (all neuroblastoma), language problems included expressive more than receptive dysfunction, and reduced speech intelligibility and output (Mitchell et al 2002). Increased later deficits, such as declining IQ, suggested a progressive encephalopathy. Mood and behavioural dysfunction, such as affective dysregulation and attention-deficit disorder, was emphasized in a subsequent report (Turkel et al 2006). Significantly reduced IQ and severe adaptive limitations, with a range of preserved neurocognitive abilities, were noted in 13 cases of mixed OMS aetiology (Papero et al 1995). These case series confirm that OMS is not a benign entity, and a substantial number of children sustain permanent brain injury.

Controversies and future directions

Only more clinical and basic research will resolve the controversies in OMS:

- Do phenotypic subgroups (paraneoplastic or postinfectious) indicate the presence of neuroimmunological subgroups?
- Is the brain injury in OMS exclusively cerebellar?
- Does aberrant connectivity develop and give rise to the comorbid features of OMS?
- What are the cellular targets of OMS in the CNS?
- Do the first clinical symptoms indicate the start of brain injury or the tip of the iceberg?
- How reversible is the brain injury? Are some children damaged beyond repair at the onset?
- Is there one instigating antigen or are there multiple antigens?

- Does a small low-stage neuroblastoma really need to be resected?
- What is the aetiology of OMS when a tumour is not found?
- Would a two-hit model of aetiopathology best fit the data (tumour or involuted tumour *plus* infection)?
- Should immunotherapy be individualized, based on biomarkers of disease activity?
- How aggressive should immunotherapy be? Do we risk fatality to prevent learning disability?
- Do any of our therapies make OMS worse?
- Should stem cell therapies be applied?

The near-future aims in OMS will be the detection and use of biomarkers to identify high-risk children, to test the efficacy of therapies, and to lay down a rational basis for investigational approaches. Application of biomarkers will allow the treatment of OMS to become evidence based. Front-end combination therapies, using biological products and drugs that work synergistically but by different mechanisms, will become the rule. Besides biomarkers of disease activity, a diagnostic biomarker would be useful for clinically atypical cases. The challenge will be to identify the underlying antigen/s in OMS so that a cure can be devised. As more immunological abnormalities are identified in OMS, careful phenotypic studies will be needed.

The sweeping advances of the future often remain outside our purview. There have been so many developments in the past 5 years relating to OMS, and so many more in the fields of immunology, oncology, and transplantation biology. Discoveries in all of these fields are likely to have implications for OMS. Certainly, therapies will become more selective and less toxic. It may even be possible to vaccinate children against neuroblastoma. We will learn more about immunoregulatory genes and how they can be manipulated to prevent autoimmune disease.

Summary and conclusions

OMS is a fascinating, although often catastrophic, autoimmune CNS disorder which is associated with neuroblastoma. It is a heterogeneous condition with varied clinical expression. So far, the only radiological and pathological abnormalities are confined to the cerebellum, especially the vermis, but the extent to which all features of OMS can be subscribed to the cerebellum remains controversial. Although a tumour is found in just under 50% of the cases, the uniform paraneoplastic theory of causation proposes that all early-onset cases are paraneoplastic, the tumour has been eradicated before OMS presents when no tumour can be found, and the multitude of diverse infectious agents that can be found are secondary triggers for the development of autoimmune disease. Frequent and heterogeneous autoantibodies to neuronal autoantigens have been found, including to postsynaptic densities and cerebellar granule neurons, but the underlying autoantigen in OMS remains elusive. Recent advances in understanding the immunopathophysiology of OMS support a role for abnormal trafficking into the CNS of the lymphocyte subsets found also to infiltrate neuroblastomas (both B cells and T cells). Although most of the research so far has focused on antineuronal autoantibodies, inflammatory chemokines (such as CXCL10) are involved in the recruitment of leucocytes into the CSF, and strongly implicate the presence of reactive astrocytosis. CSF BAFF levels

correlate with autoantibodies and are lowered by ACTH and steroids. Therapeutic implications abound. Abnormal B-cell trafficking into the CNS already has been interrupted by cell-specific immunotherapy, such as the anti-CD20 monoclonal antibody rituximab, with clinical benefit. Future therapies may be directed at blocking other leucocytes, autoantibodies, or cytokines. The chronic relapsing subgroup of OMS continues to be a challenge and requires sedulous research. For now, early, front-end multimodal immunotherapy, combining conventional agents and some form of chemotherapy, seems to afford the best chance for neurological remission and good outcome.

Acknowledgements

The NPMC is currently funded by grants from the William E. McElroy Charitable Foundation (Springfield, IL), the Chicago Institute of Neurosurgery and Neuroresearch Foundation (Chicago, IL), Spastic Paralysis and Allied Diseases of the Central Nervous System Research Foundation (Illinois-Eastern Iowa District, Kiwanis International), the Thrasher Research Fund (Salt Lake City, UT), Ronald McDonald House Charities (Central Illinois, IL), Questcor Pharmaceuticals (Union City, CA), and Genetech/Biogen IDEC (San Francisco, CA).

REFERENCES

- Altmann AJ, Baehner RL (1976) Favorable prognosis for survival in children with coincident opso-myoclonus and neuroblastoma. *Cancer* 37: 846–52.
- Antunes NL, Khakoo Y, Matthay KK et al (2000) Antineuronal antibodies in patients with neuroblastoma and paraneoplastic opsoclonus-myoclonus. *J Pediatr Hematol Oncol* 22: 315–20.
- Armstrong MB, Robertson PL, Castle VP (2005) Delayed, recurrent opsoclonus-myoclonus syndrome responding to plasmapheresis. *Pediatr Neurol* 33: 365–7.
- Arnsten AF (2006) Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. *J Clin Psychiatry* 67(Suppl 8): 7–12.
- Bartoš A (2006) Effective high-dose clonazepam treatment in two patients with opsoclonus and myoclonus: GABAergic hypothesis. *Eur Neurol* 56: 240–2.
- Bataller L, Rosenfeld MR, Graus F, Vilchez JJ, Cheung NK, Dalmau J (2003) Autoantigen diversity in the opsoclonus-myoclonus syndrome. *Ann Neurol* 53: 347–53.
- Beck S, Fühlhuber V, Krasenbrink I et al (2007) IgG subclass distribution of autoantibodies in pediatric opsoclonus-myoclonus syndrome. *J Neuroimmunol* 185: 145–9.
- Blaes F, Fühlhuber V, Korfei M et al (2005) Surface-binding autoantibodies to cerebellar neurons in opsoclonus syndrome. *Ann Neurol* 58: 313–17.
- Blüml S, Chen V, Panigraphy A (2006) Neuroimaging of opsoclonus-ataxia sequelae: MRS and voxel-based morphometry. *Ann Neurol* 60(Suppl 3): S156.
- Bolthausen E, Deonna T, Hirt HR (1979) Myoclonic encephalopathy of infants or ‘dancing eyes syndrome.’ *Helv Paediatr Acta* 34: 119–33.
- Botez MI, Botez T, Elie R, Attig E (1989) Role of the cerebellum in complex human behavior. *Ital J Neurol Sci* 10: 291–300.
- Boubaker A, Bischof Delaloye A (2003) Nuclear medicine procedures and neuroblastoma in childhood: their value in the diagnosis, staging and assessment of response to therapy. *Q J Nucl Med* 47: 31–40.
- Candler PM, Dale RC, Griffin S et al (2006) Post-streptococcal opsoclonus-myoclonus syndrome associated with anti-neuroleukin antibodies. *J Neurol Neurosurg Psychiatry* 77: 507–12.
- Cardesa-Salzmann TM, Mora J, Garcia Cazorla MA, Crus O, Muñoz C, Campistol J (2006) Epstein-Barr virus related opsoclonus-myoclonus-ataxia does not rule out the presence of occult neuroblastoma tumors. *Pediatr Blood Cancer* 47: 964–7.
- Chemli J, Ketata S, Dalhoumi A et al (2007) Opsoclonus-myoclonus syndrome associated with Mycoplasma pneumoniae infection. *Arch Pediatr* 14: 1003–6.

- Clerico A, Tenore A, Bartolozzi S et al (1993) Adrenocorticotrophic hormone-secreting ganglioneuroblastoma associated with opsomyoclonic encephalopathy: a case report with immunohistochemical study. *Med Pediatr Oncol* 21: 690–4.
- Connolly AM, Pestronk A, Mehta S, Pranzatelli MR, Noetzel MJ (1997) Serum autoantibodies in childhood opsoclonus-myoclonus syndrome: an analysis of antigenic targets in neural tissues. *J Pediatr* 130: 878–84.
- Cooper R, Khakoo Y, Matthay KK et al (2001) Opsoclonus-myoclonus-ataxia syndrome in neuroblastoma: histopathologic features: a report from the children's cancer group. *Med Pediatr Oncol* 36: 623–9.
- Darnell RB, Posner JB (2006) Paraneoplastic syndromes affecting the nervous system. *Semin Oncol* 33: 270–98.
- Davidson A, Diamond B (2001) Autoimmune diseases. *N Engl J Med* 345: 340–50.
- Ertle F, Behnisch W, Al Mulla NA et al (2008) Treatment of neuroblastoma-related opsoclonus-myoclonus-ataxia syndrome with high-dose dexamethasone pulses. *Pediatr Blood Cancer* 50: 683–7.
- Everson TC, Cole WH (1966) Spontaneous regression of neuroblastoma. In: Everson TC, Cole WH (editors). *Spontaneous Regression of Cancer*. Philadelphia, PA: WB Saunders.
- Feasby T, Banwell B, Benstead T et al (2007) Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 21(2 Suppl 1): S57–107.
- Fuchs AF, Kaneko CRS, Seudder CA (1985) Brainstem control of saccadic eye movements. *Annu Rev Neurosci* 8: 307–37.
- Fühlber V, Bicks S, Kirsten A et al (2009) Elevated B-cell activating factor BAFF, but not APRIL, correlates with CSF cerebellar autoantibodies in pediatric opsoclonus-myoclonus syndrome. *J Neuroimmunol* 210: 87–91.
- Gambini C, Conte M, Bernini G et al (2003) Neuroblastic tumors associated with opsoclonus-myoclonus syndrome: histological, immunohistochemical and molecular features of 15 Italian cases. *Virchows Arch* 442: 555–62.
- Gesundheit B, Smith CR, Gerstle JT, Weitzman SS, Chan HS (2004) Ataxia and secretory diarrhea: two unusual paraneoplastic syndromes occurring concurrently in the same patient with ganglioneuroblastoma. *J Pediatr Hematol Oncol* 26: 549–52.
- Hamilton NG, Frick RB, Takahasi T, Hopping MW (1983) Psychiatric symptoms and cerebellar pathology. *Am J Psychiat* 140: 1322–6.
- Hammer MS, Larsen MB, Stack CV (1995) Outcome of children with opsoclonus-myoclonus regardless of etiology. *Pediatr Neurol* 13: 21–4.
- Hayward K, Jeremy RJ, Jenkins S et al (2001) Long-term neurobehavioral outcomes in children with neuroblastoma and opsoclonus-myoclonus-ataxia syndrome: relationship to MRI findings and anti-neuronal antibodies. *J Pediatr* 139: 552–9.
- Hickey WF (1999) Leukocyte traffic in the central nervous system: the participants and their roles. *Semin Immunol* 11: 125–37.
- Honnorat J, Antoine JC (2007) Paraneoplastic neurological syndromes. *Orphanet J Rare Dis* 2: 22.
- Jones CE, Smyth DP, Faust SN (2007) Opsoclonus-myoclonus syndrome associated with group A streptococcal infection. *Pediatr Infect Dis J* 26: 358–9.
- Kinsbourne M (1962) Myoclonic encephalopathy of infants. *J Neurol Neurosurg Psychiatry* 25: 221–76.
- Kirsten A, Beck S, Fühlhuber V et al (2007) New autoantibodies in pediatric opsoclonus myoclonus syndrome. *Ann N Y Acad Sci* 1110: 256–60.
- Klein A, Schmitt B, Boltshauser E (2007) Long-term outcome of ten children with opsoclonus-myoclonus syndrome. *Neuropediatrics* 166: 359–63.
- Koh PS, Raffensperger JG, Berry S et al (1994) Long-term outcome in children with opsoclonus-myoclonus and ataxia and coincident neuroblastoma. *J Pediatr* 125: 712–16.
- Koh S, Turkel SB, Baram TZ (1997) Cerebellar mutism in children: a report of six cases and potential mechanisms. *Pediatr Neurol* 16: 218–19.
- Korfei M, Fühlhuber V, Schmidt-Woll T et al (2005) Functional characterisation of autoantibodies from patients with pediatric opsoclonus-myoclonus-syndrome. *J Neuroimmunol* 170: 150–7.
- Krumbholz M, Theil D, Derfuss T et al (2005) BAFF is produced by astrocytes and up-regulated in multiple sclerosis lesions and primary central nervous system lymphoma. *J Exp Med* 201: 195–200.
- Kuban KC, Ephros MA, Freeman RL, Laffell LB, Bresnan MJ (1983) Syndrome of opsoclonus-myoclonus caused by Coxsackie B3 infection. *Ann Neurol* 13: 69–71.
- Kuhn MJ, Pranzatelli MR, Langheim JM (2002) MR Spectroscopy in children with opsoclonus-myoclonus syndrome. Proceedings from the 40th Annual Meeting of the American Society of Neuroradiology, Vancouver, Canada, p. 233.

- Lalonde R, Botez MI (1990) The cerebellum and learning processes in animals. *Brain Res Rev* 15: 325–32.
- Lieberman P (2002) On the nature and evolution of the neural bases of human language. *Am J Phys Anthropol* 35(Suppl): 36–62.
- McGarvey CK, Applegate K, Lee ND, Sokol DK (2006) False-positive metaiodobenzylguanidine scan for neuroblastoma in a child with opsoclonus-myoclonus syndrome treated with adrenocorticotropic hormone (ACTH). *J Child Neurol* 21: 606–10.
- McMinn P, Stratov I, Nagarajan L, Davis S (2001) Neurological manifestations of enterovirus 71 infection in children during an outbreak of hand, foot, and mouth disease in Western Australia. *Clin Infect Dis* 32: 236–42.
- Manley GT, Smitt PS, Dalmau J, Posner JB (1995) Hu antigens: reactivity with Hu antibodies, tumor expression, and major immunogenic sites. *Ann Neurol* 38: 102–110.
- Marr D (1969) A theory of cerebellar cortex. *J Physiol* 202: 437–470.
- Martin EF, Beckwith JB (1968) Lymphoid infiltrates in neuroblastoma: their occurrence and prognostic significance. *J Pediatr Surg* 3: 161–4.
- Mink JW, Caruso PA, Pomeroy SL (2003) Progressive myoclonus in a child with a deep cerebellar mass. *Neurology* 61: 829–31.
- Mitchell WG, Davalos-Gonzalez Y, Brumm VL, Aller SK, Burger E, Turkel SB, Borchert MS, Hollar S, Padilla S (2002) Opsoclonus-ataxia caused by childhood neuroblastoma: developmental and neurologic sequelae. *Pediatrics* 109: 86–98.
- Nishihira H, Toyoda Y, Tanaka Y et al (2000) Natural course of neuroblastoma detected by mass screening: a 5-year prospective study at a single institution. *J Clin Oncol* 18: 3012–17.
- Oguro K, Kobayashi J, Aiba H, Hojo H (1997) Opsoclonus-myoclonus syndrome with abnormal single photon emission computed tomography imaging. *Pediatr Neurol* 16: 334–6.
- Papero PH, Pranzatelli MR, Margolis LJ, Tate E, Wilson LA, Glass P (1995) Neurobehavioral and psychosocial functioning of children with opsoclonus-myoclonus syndrome. *Dev Med Child Neurol* 37: 915–32.
- Petruzzini JM, DeAlarcon PA (1995) Neuroblastoma-associated opsoclonus-myoclonus treated with intravenously administered immune globulin G. *J Pediatr* 127: 328–9.
- Pohl KRE, Pritchard J, Wilson J (1996) Neurological sequelae of the dancing eye syndrome. *Eur J Pediatr* 155: 237–44.
- Pranzatelli MR (1992) The neurobiology of opsoclonus-myoclonus. *Clin Neuropharmacol* 15: 186–228.
- Pranzatelli MR (1994) On the molecular mechanism of adrenocorticotropic hormone: neurotransmitters and receptors. *Exp Neurol* 125: 142–61.
- Pranzatelli MR (1996) The immunopharmacology of the opsoclonus-myoclonus syndrome. *Clin Neuropharmacol* 19: 1–47.
- Pranzatelli MR (2000a) Paraneoplastic syndromes: an unsolved murder. *Sem Ped Neurol* 7: 118–30.
- Pranzatelli MR (2000b) Friendly Fire. *Discover* April: 35–6.
- Pranzatelli MR (2005) Opsoclonus-myoclonus-ataxia syndrome. In: Fernández-Alvarez E, Arzimanoglou A, Tolosa E, editors. *Paediatric Movement Disorders. Progress in Understanding*. John Libbey Eurotext, p. 121–136.
- Pranzatelli MR, Balletti J (1992) Serotonin receptors in human neuroblastoma: a possible biologic tumor marker. *Exp Neurol* 115: 423–7.
- Pranzatelli MR, Kao PC, Tate ED et al (1993) Antibodies to ACTH in opsoclonus-myoclonus. *Neuropediatrics* 24: 131–3.
- Pranzatelli MR, Huang Y, Tate E et al (1995) Cerebrospinal fluid 5-hydroxyindoleacetic acid and homovanillic acid in the pediatric opsoclonus-myoclonus syndrome. *Ann Neurol* 37: 189–97.
- Pranzatelli MR, Huang Y, Tate E et al (1998a) Monoaminergic effects of high-dose corticotropin in corticotropin-responsive pediatric opsoclonus-myoclonus. *Mov Disord* 13: 522–8.
- Pranzatelli MR, Hanin I, Tate E et al (1998b) Cerebrospinal fluid free choline in movement disorders of pediatric onset. *Eur J Ped Neurol* 1: 33–9.
- Pranzatelli MR, Tate E, Huang Y, Baldwin M (1994) Clinical responses to 5-hydroxy-L-tryptophan in chronic pediatric opsoclonus-myoclonus suggest biochemical heterogeneity: a double-blinded placebo crossover pilot study. *Clin Neuropharmacol* 17: 103–16.
- Pranzatelli MR, Tate ED, Galvan I, Wheeler A (2001) Controlled pilot study of piracetam for pediatric opsoclonus-myoclonus. *Clin Neuropharmacol* 24: 352–7.

- Pranzatelli MR, Tate ED, Kinsbourne M, Caviness Jr VS, Mishra B (2002a) Forty-one year follow-up of childhood-onset opsoclonus-myoclonus: cerebellar atrophy, multiphasic relapses, response to IVIG. *Mov Disord* 17: 1387–90.
- Pranzatelli MR, Tate ED, Wheeler A et al (2002b) Screening for autoantibodies in children with opsoclonus-myoclonus-ataxia. *Ped Neurol* 27: 384–387.
- Pranzatelli MR, Tate ED, Travelstead AL, Verhulst SJ (2003) CSF B-cell over-expansion in paraneoplastic opsoclonus-myoclonus: effect of rituximab, an anti-B-cell monoclonal antibody. *Neurology* 60(Suppl 1): S395.
- Pranzatelli MR, Hyland K, Tate ED, Arnold LA, Allison TJ, Soori GS (2004a) Evidence of cellular immune activation in children with opsoclonus-myoclonus: cerebrospinal fluid neopterin. *J Child Neurol* 19: 919–24.
- Pranzatelli MR, Travelstead A, Tate ED et al (2004b) B- and T-cell markers in opsoclonus-myoclonus syndrome: immunophenotyping of CSF lymphocytes. *Neurology* 62: 1526–32.
- Pranzatelli MR, Travelstead AL, Tate ED et al (2004c) Immunophenotype of blood lymphocytes in neuroblastoma-associated opsoclonus-myoclonus. *J Pediatr Hematol Oncol* 26: 718–23.
- Pranzatelli MR, Tate ED, Dukart WS, Flint MJ, Hoffman MT, Oksa AE (2005a) Sleep disturbance and rage attacks in opsoclonus-myoclonus syndrome: response to trazodone. *J Pediatr* 147: 372–8.
- Pranzatelli MR, Chun KY, Moxness M, Tate ED, Allison TJ (2005b) Cerebrospinal fluid ACTH and cortisol in opsoclonus-myoclonus: effect of therapy. *Pediatr Neurol* 33: 121–6.
- Pranzatelli MR, Tate ED, Travelstead AL, Grana N, Parkhurst J, Russell C (2005c) Cyclophosphamide therapy in pediatric opsoclonus-myoclonus syndrome. *Ann Neurol* 58(Suppl 9): S90.
- Pranzatelli MR, Tate ED, Travelstead AL, Longee D (2005d) Immunologic and clinical response to rituximab in a child with opsoclonus-myoclonus syndrome. *Pediatrics* 115: e115–19.
- Pranzatelli MR, Tate ED, Travelstead AL, Bennett HJ, Kerstan P, Sharpe S (2005e) Mycophenolate reduces CSF T-cell activation and is a steroid sparer in opsoclonus-myoclonus syndrome. *Ann Neurol* 58(Suppl 9): S111.
- Pranzatelli MR, Tate ED, Travelstead AL et al (2006) Rituximab (anti-CD20) adjunctive therapy for opsoclonus-myoclonus syndrome. *J Pediatr Hematol Oncol* 28: 585–93.
- Pranzatelli MR, Tate ED, Hoefgen E, Verhulst SJ (2007) Interferon-inducible protein 10 (CXCL10) is increased in the cerebrospinal fluid of children with opsoclonus-myoclonus syndrome. *Ann Neurol* 62(Suppl 11): S112–13.
- Pranzatelli MR, Tate ED, Crowley JR, Toennies B, Creer M (2008a) Neurometabolic effects of ACTH on free amino compounds in opsoclonus-myoclonus syndrome. *Neuropediatrics* 39:164-171.
- Pranzatelli MR, Tate ED, Hoefgen E, Swan J, Colliver JA (2008b) Therapeutic down-regulation of central and peripheral B-cell activating factor (BAFF) production in opsoclonus-myoclonus. *Cytokine* 44: 26–32.
- Pranzatelli MR, Tate ED, Travelstead AL et al (2009) Insights on chronic-relapsing opsoclonus-myoclonus from a pilot study of mycophenolate mofetil. *J Child Neurol* 24: 316–22.
- Riva D, Giorgi C (2000) The cerebellum contributes to higher functions during development. *Brain* 123: 1051–61.
- Rudnick E, Khakoo Y, Antunes NL et al (2001) Opsoclonus-myoclonus-ataxia syndrome in neuroblastoma: clinical outcome and antineuronal antibodies – a report from the Children’s Cancer Group Study. *Med Pediatr Oncol* 36: 612–22.
- Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. *Brain* 121: 561–79.
- Shalaby-Rana E, Majd M, Andrich MP, Movassaghi N (1997) In-11 pentetretotide scintigraphy in patients with neuroblastoma. Comparison with I-131 MIBG, N-Myc oncogene amplification, and patient outcome. *Clin Nucl Med* 22: 315–19.
- Smith JW (1997) Apheresis techniques and cellular immunomodulation. *Ther Apher* 1: 203–6.
- Solomon GE, Chutorian AM (1968) Opsoclonus and occult neuroblastoma. *N Engl J Med* 279: 475–7.
- Sorenson T, Tani M, Jensen J et al (1999) Expression of specific chemokines and chemokine receptors in the central nervous system of multiple sclerosis patients. *J Clin Invest* 106: 807–15.
- Sugie H, Sugie Y, Akimoto H, Endo K, Shirai M, Ito M (1992) High-dose IV human immunoglobulin in a case with infantile opsoclonus polymyoclonia syndrome. *Acta Paediatr* 18: 371–2.
- Talon P, Stoll C (1985) Opso-myoclonus syndrome of infancy. New observations: review of literature (110 cases). *Pédiatrie* 40: 441–9.
- Tate ED, Pranzatelli MR, Huang Yy et al (1994) An innovative approach to the problem of sedating children with opsoclonus-myoclonus syndrome: effects of myoclonus and CSF monoamine metabolites. *Ann Neurol* 36: 543–4.

- Tate ED, Allison TJ, Pranzatelli MR, Verhulst SJ (2005) Neuroepidemiologic trends in 105 cases of pediatric opsoclonus-myoclonus syndrome. *J Pediatr Oncol Nurs* 22: 8–19.
- Tate ED, Pranzatelli MR, Harber JA et al (2007) Pharmacokinetic and time-course study of rituximab in pediatric opsoclonus-myoclonus syndrome. *Ann Neurol* 62 (Suppl 11): S113.
- Tersak JM, Safier RA, Schor NF (2005) Rituximab (anti-CD20) in the treatment of refractory neuroblastoma-associated opsoclonus-myoclonus syndrome. *Ann Neurol* 58: S111.
- Tuchman RF, Alvarez LA, Kantrowitz AB, Moser FG, Llena J, Moshé SL (1989) Opsoclonus-myoclonus syndrome: correlation of radiographic and pathologic observations. *Neuroradiology* 31: 250–2.
- Turkel SB, Brumm VL, Mitchell WG, Tavare CJ (2006) Mood and behavioral dysfunction with opsoclonus-myoclonus ataxia. *J Neuropsychiatry Clin Neurosci* 18: 239–41.
- van Toorn R, Rabie H, Warwick JM (2005) Opsoclonus-myoclonus in an HIV-infected child on antiretroviral therapy: possible immune reconstitution inflammatory syndrome. *Eur J Paediatr Neurol* 9: 423–426.
- Veneselli E, Conte M, Biancheri R, Acquaviva A, De Bernardi B (1998) Effect of steroid and high-dose immunoglobulin therapy on opsoclonus-myoclonus syndrome occurring in neuroblastoma. *Med Pediatr Oncol* 30: 15–17.
- Wertenbaker C, Behrens MM, Hunter SB, Plank CR (1981) Opsoclonus: a cerebellar disorder? *Neuro-Ophthalmology* 2: 73–84.
- Wikberg JE, Muceniece R, Mandrika I et al (2000) New aspects on the melanocortins and their receptors. *Pharmacol Res* 42: 393–420.
- Wilken B, Baumann M, Bien CG, Hero B, Rostasy K, Hanefeld F (2008) Chronic relapsing opsoclonus-myoclonus syndrome: combination of cyclophosphamide and dexamethasone pulses. *Eur J Paediatr Neurol* 12: 51–5.
- Wong A (2007) An update on opsoclonus. *Curr Opin Neurol* 20: 25–31.
- Yiu VW, Kovithavongs T, McGonigle LF, Ferreira P (2001) Plasmapheresis as an effective treatment for opsoclonus-myoclonus syndrome. *Pediatr Neurol* 24: 72–4.
- Ziter FA, Bray PF, Cancilla PA (1979) Neuropathological findings in a patient with neuroblastoma and myoclonic encephalopathy. *Arch Neurol* 36: 51.