Diagnosis and Management of Opsoclonus-Myoclonus-Ataxia Syndrome in Children: An International Perspective

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on behalf of the OMS Study Group

47 physicians/scientist from 37 institutions and 12 parent and patients from OMS life and DES Trust

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Consensus Recommendations

- Clinical evaluation
- Investigations (including biomarkers)
- Neuroblastoma treatment
- Immunotherapy
- Monitoring outcome
- Vaccination and re-vaccination

Demographics

- First described in 1967 by Kinsbourne in a series of 6 children with a ‘myoclonic encephalopathy’
- UK incidence reported as 0.18 cases per million of the population

Ki Pang et al. 2010 ***Eur J Paediatr Neurol*** 14(2):156-161

- Majority presenting before 5 (mean age of onset 18m; median 16.5m)
- Affect boys and girls equally but recent data report more girls (60%)

Sheridan A, et al. 2020 ***Dev Med Child Neurol*** 62(12):1444-1449.

Diagnostic criteria

Genoa criteria

Cancer Letters 2005; 228 275–282

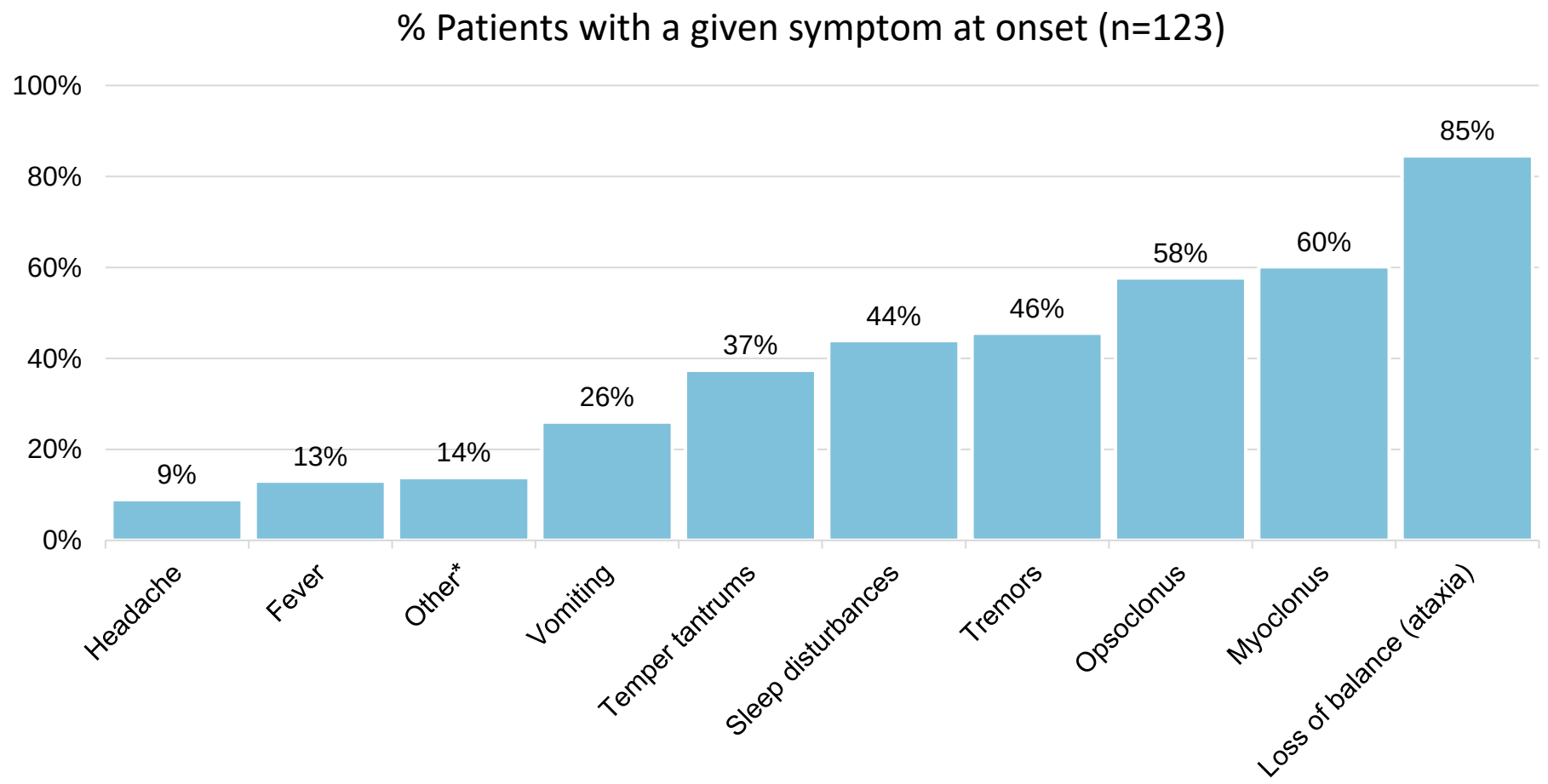
- Opsoclonus
- Myoclonus / ataxia
- Behavioral change and/or sleep disturbance
- Neuroblastoma

3 out of 4 features

Opsoclonus

- Involuntary, arrhythmic, chaotic, and multidirectional eye movements
- May be brief, transient
- May be elicited by the ‘squeeze test’
- May develop initially as ocular flutter (bursts of saccades in the horizontal plane during forward fixation)

Ataxia most common symptom at onset in OMAS Patient Reported Natural History Study



OMS life Foundation

Slide courtesy Of Michael Michaelis (PI); Funded by National Organization of Rare Diseases and US FDA

OMAS scoring

- Opsoclonus Myoclonus Evaluation Scale of Motor Performance
  - 12 domains
  - 0-3
- Validated and correlated with biomarkers and outcome
- Lengthy and only motor

Pranzatelli et al., 2001 ***Clin Neuropharm*** 24: 3527

- Mitchell and Pike OMS Rating scale
  - 5/6 domains (stance, gait, arm/hand function, opsoclonus, mood/behaviour +/- speech)
  - 0-3
- Easier to use and more widely adopted
- Still requires formal validation

De Grandis et al., 2009 ***Neuropediatrics*** 40(3):103-11

Table 4 Mitchell and Pike OMS Rating Scale

Stance	0	Standing and sitting balance normal for age
	1	Mildly unstable standing for age, slightly wide based
	2	Unable to stand without support but can sit without support
	3	Unable to sit without using hands to prop or other support
Gait	0	Walking normal for age
	1	Mildly wide-based gait for age, but able to walk indoors and outdoors independently
	2	Walks only or predominantly with support from person or equipment
	3	Unable to walk even with support from person or equipment
Arm/hand function	0	Normal for age
	1	Mild, infrequent tremor or jerkiness without functional impairment
	2	Fine motor function persistently impaired for age, but less precise manipulative tasks normal or almost normal
	3	Major difficulties in all age-appropriate fine motor and manipulative tasks
Opsoclonus	0	None
	1	Rare or only when elicited by change in fixation or squeeze test
	2	Frequent, interferes intermittently with fixation or tracking
	3	Persistent, interfering continuously with function and tracking
Mood/behavior	0	Normal
	1	Mild increase in irritability but consolable and/or mild sleep disturbances
	2	Irritability and sleep disturbances interfering with child and family life
	3	Persistent severe distress
Speech	0	Normal for age, no loss
	1	Mildly unclear, plateaued in development
	2	Loss of some words or some grammatical constructs (i.e., from sentences to phrases) but still communicates verbally
	3	Severe loss of verbal communication and speech.

Abbreviation: OMS = opsoclonus-myoclonus syndrome.

Tumour

- Peripheral neuroblastic tumour in around 50% of children with OMAS – most commonly neuroblastoma
- OMAS in 2-3% of Neuroblastoma
- Presence or absence of tumour does not alter OMAS prognosis
- Identification of tumour crucial to successful treatment

Investigations

- Key is excluding other diagnosis
  - ➢ May identify infectious trigger
- Identifying neuroblastoma
- Defining level of inflammation

Table 2 Recommendations for Initial Investigations of Children With OMAS

Blood tests	➢ Full blood count, Erythrocyte sedimentation rate, electrolytes, urea, uric acid, lactate, creatinine, C-reactive protein, liver function tests, glucose (with paired CSF), clotting studies (international normalized ratio and partial thromboplastin time), IgG/IgM and albumin synthesis index (with paired CSF), and infectious studies to identify potential trigger (with CSF if indicated), immunophenotyping by FACS for B cell subsets if available, IgG, IgA, IgM
Infection screening	➢ PCR and/or serology for herpes viruses (CMV, EBV, VZV, HHV-6), West Nile virus, adenovirus, enterovirus and influenza in blood, CSF, stool and nasopharyngeal aspirate as indicated by clinical circumstances
CSF	➢ Cell count, protein level, glucose (with paired blood glucose to exclude glucose transporter defect), lactate, IgG and albumin synthesis index (with paired blood sample), oligoclonal bands (with paired serum), immunophenotyping by FACS for B cell subsets if available, neopterins if available (neurotransmitter panel)
Neuroimaging	MRI Brain to exclude focal lesion in the posterior fossa
Laboratory screening for neuroblastoma	➢ Urine catecholamine metabolites. If not available on random urine (as opposed to 24 hours collection) this may be deferred pending imaging results. ➢ Serum: neuron specific enolase (NSE) and lactate dehydrogenase (LDH) ➢ N.B: consider other tumors including screening for antibodies such as anti-Hu/ANNA1 antibodies
Imaging for neuroblastoma	Whole body imaging should be performed in all children with OMS. Where there may be delay in obtaining whole body magnetic resonance imaging, first-line imaging comprising chest x-ray, abdominal ultrasound, and MIBG scintigraphy may be performed, proceeding to whole body imaging if no neuroblastoma is identified. The following MRI sequences are recommended: 4-mm sections of regions typically affected by neuroblastoma: ➢ Abdomen/pelvis: Axial T1-w, T2-w, T2-w fat suppression; coronal T2-w; sagittal (spine) T1-w, T2-w, T2-w fat suppression ➢ Chest: Axial T1-w, T2-w; coronal: T2-w; sagittal (spine) T1-w, T2-w, T2-w fat suppression ➢ Axial T1-w, T2-w; sagittal (spine) T1-w, T2-w, T2-w fat suppression N.B.: If a tumor is suspected in one of the native investigations, T1-w contrast-enhanced sequence of that investigation (abdomen, chest, or neck) should be added. An equivalent CT protocol may be used following consideration of the above.

Abbreviations: CMV = cytomegalovirus; EBV = Epstein Barr virus; FACS = fluorescence activated cell sorting; HHV-6 = human herpes virus 6; Ig = immunoglobulin; OMAS = opsoclonus-myoclonus-ataxia syndrome; VZV = varicella zoster virus.

Neuroblastoma screening

- Urine catecholamines metabolites (VMA/HVA)
  - Spot urine more practical than 24 hour collection
  - Tumours often small and non-secreting therefore yield may be low (24%)

Biasotti et al. ***Med Pediatr Oncol*** 2000;**35**(2):153-155

- Serum specific enolase and lactate dehydrogenase may be elevated
- Consider other paraneoplastic antibodies (Anti Hu/ANNA1 antibodies)

Neuroblastoma imaging

- Non-axial imaging
  - CXR/US has limited sensitivity, but may have a role while axial imaging awaited
- CT
  - No evidence of inferiority to MR but requires pre and post contrast imaging with significant radiation load
- MIBG
  - Highly specific, but false negative rate up to 24%

    Biasotti S et al. ***Med Pediatr Oncol*** 2000;**35**(2):153-155.
- MRI
  - Sensitivity up to 100% in some studies
  - Requires high resolution and an experienced paediatric radiologists

Investigations – key management points

- MRI vs MIBG vs Xray/US
- Important to make sure all investigations for immuno-surveillance performed
- Initiation of OMAS treatment prior to completion of investigation
  - ➢ Once alternatives with different treatments excluded

Courtesy of Dr Paola Angelini
Royal Marsden Hospital

International Neuroblastoma Risk Group stratification

Table 2. International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

NOTE. See text for detailed criteria. Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.

J Clin Oncol. 2009 27(2): 298–303

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS	< 18			NA	No		C Very low
					Yes		Q High
				Amp			R High

J Clin Oncol. 2009 27(2): 289–297

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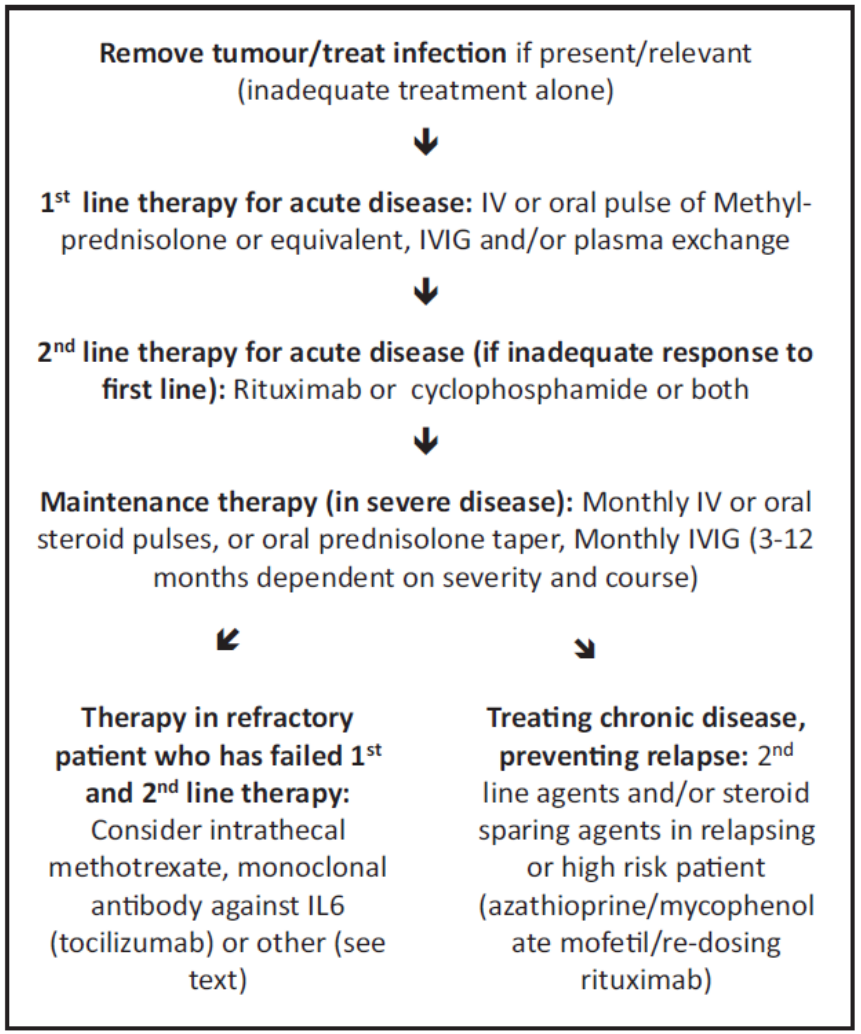
Courtesy of Dr Paola Angelini
Royal Marsden Hospital

Treatment at glance

Stage	Age (mo.)	MYCN	Grade	CA	LTS	Risk group	Courses	Treatment	LINES [1]
L1	all	Non-amp				Low	0	Surgery/observation only	
L1	all	Amp				Intermediate	6	Carbo/etop and CADO x6 cycles total ± surgery + radiotherapy + cis-RA	9
L2	≤18	Non-amp		NCA	no LTS	Low	0	Observation ± surgery	1
L2	≤18	Non-amp		NCA	LTS	Low	2-4	Carbo/etop x2-4 ± CADO x2 ± surgery	2
L2	≤18	Non-amp		SCA		Low	4	Carbo/etop x2-4 ± CADO x2 ± surgery	3
L2	>18	Non-amp	Diff [2]			Intermediate	4	Carbo/etop x2 + (CADO x2 or carbo/etop x2) ± surgery	7
L2	>18 > 5 yrs [3]	Non-amp	Undiff			Intermediate	6	Carbo/etop and CADO x6 cycles total ± surgery + radiotherapy + cis-RA	8
L2	>5 yrs	Non-amp	Undiff			Intermediate		Particular consideration should be given to these patients, high-risk therapy may be warranted. Please discuss with national coordinators	
L2	All	Amp				High		High-risk study	
M	<12	Non-amp				Intermediate	4-8	Carbo/etop x2-4 ± CADO x2-4 ± surgery	10
M	12-18	Non-amp		NCA		Intermediate		High-risk study but receive only COJEC and surgery [4]	
M	12-18	Non-amp		SCA		High		High-risk study	
M	>18	Non-amp				High		High-risk study	
M	All	Amp				High		High-risk study	
Ms	≤12	Non-amp		NCA	no LTS	Low	0	Observation only	4
Ms	≤12	Non-amp		NCA	LTS	Low	2-4	Carbo/etop x2-4 ± CADO x2	5
Ms	≤12	Non-amp		SCA		Low	4	Carbo/etop x2-4 ± CADO x2 ± surgery	6
Ms	≤12	Amp				High		High-risk study	

Management

- Immunotherapy
  - ➢No clear optimal treatment
  - ➢Front loaded vs stepwise escalation
- Symptom management
- Monitoring



Early and adequate immunotherapy improves outcome in neuroinflammation

Nosadini et al., 2015 ***Expert Rev Neurother*** 15(12):1391-419

Dale et al., 2017 ***Curr Opin Neurol***. 30(3):334-344

Wells and Hacohen et al., 2018 ***Nat Rev Neurol.*** 14(7):433-445

OMS

Average time to diagnosis is 11 weeks

Worse outcome in delay more that 2 months

Tate ED, et al., 2005 J Pediatr Oncol Nurs 22:8-19

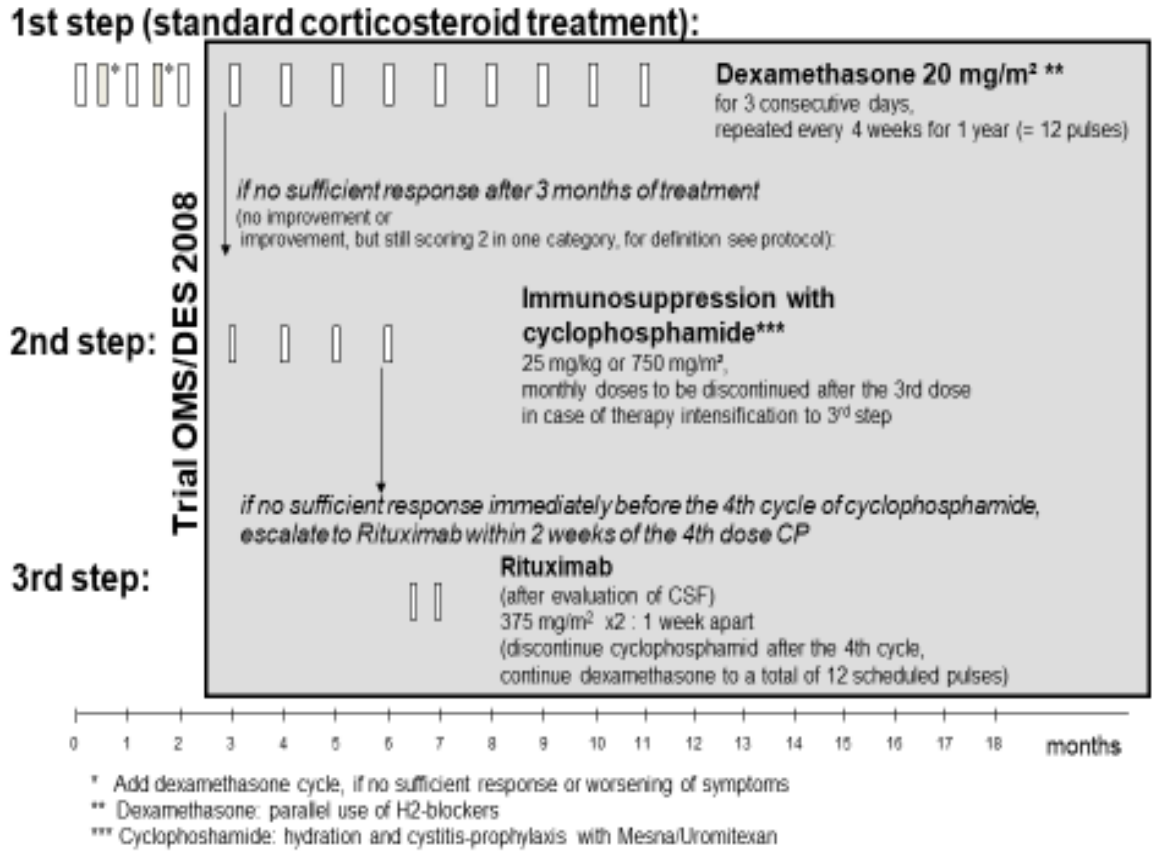
DeGrandis E, et al. 2009 Neuropediatrics 40:103-110

Front loaded

Steroid therapy (ACTH or corticosteroids) for one year
+
IVIG
+
Cyclophosphamide OR Rituximab

Pranzatelli et al., 2010
Movement Disorders 2010; 25: 238-242

EU Protocol



EU Trial ***NCT01868269***

J. Neurol. Neurosurg. Psychiat., 1962, **25**, 271

Myoclonic encephalopathy of infants

M. KINSBOURNE

From the Hospital for Sick Children, Great Ormond Street, London

Case 2 17m 40mg OD prednisolone relapsing course over 3 years

Case 3 10m 20mg OD on weaning relapsed @ 2 weeks; 3 relapses started ACTH (complete remission)

Case 4 3yrs (presented 18m) 40mg OD after 10 days ACTH effective from 48 hours and symptom free 10 days

Case 5 10m ACTH single injection total resolution; continued for 2 weeks; relapsed within 1 week and ACTH controlled again but after relapse subtle motor deficit

Case 6 16m Prior to admission started steroids. ACTH superior effect. Continued ACTH

What is a therapeutic window?

- Natural history of disease
- **What time course are we intervening at?**

Steroid-responsive encephalomyelitis in childhood

Joseph F. Pasternak, M.D., Darryl C. De Vivo, M.D., and Arthur L. Prensky, M.D.

NEUROLOGY 30: 481-486, **May 1980**

expected to respond more favorably to therapeutic manipulation than would the more fulminant picture of "measles encephalitis." It is difficult to document the natural history of this subacute syndrome because similar slowly progressive cases have been reported infrequently. It is clear that the potential for spontaneous recovery does exist, although these patients can be left with significant sequelae.[19-21] We withheld therapy in six of our seven patients for from 2 to 4 weeks despite further neurologic deterioration. It is possible that our patients eventually would have recovered spontaneously, but the immediate cessation of progression in each patient upon initiation of corticosteroid therapy, followed by continuous improvement until they fully recovered, implies that steroids limited morbidity and facilitated recovery. The apparent relapse of patient 2 after a brief 3-day course of steroid therapy further supports this belief. An appropriately designed control study would be necessary to document the apparent therapeutic value of corticosteroids in this syndrome.

Better outcome if Rituximab used and used earlier

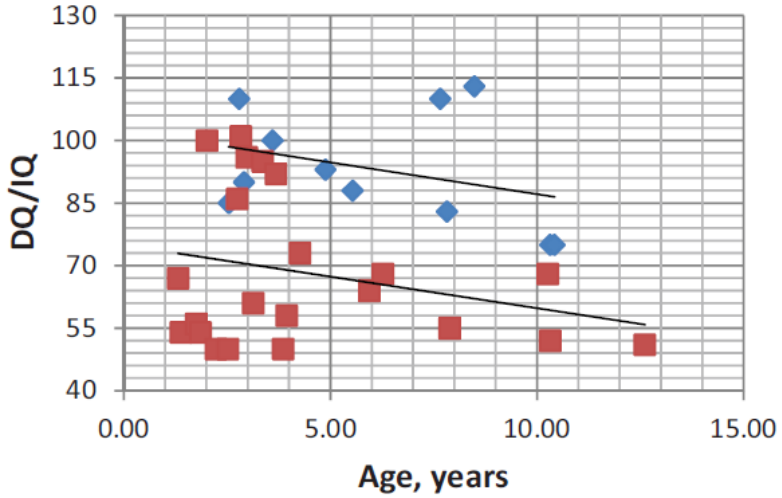
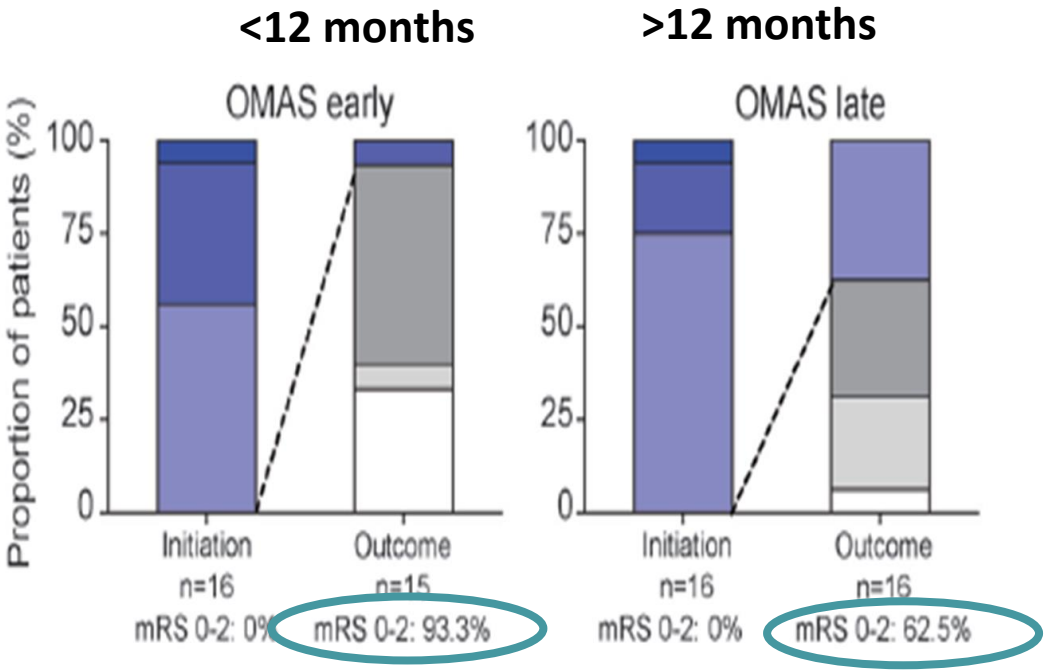


Table 3. Comparison of Treatment of the Old and New Groups.

Group (n)	Age onset (mo)	Interval to diagnosis (mo)	Interval ≤2 mo (%)	Interval >2 mo (%)	ACTH (n)	Oral steroids (n)	IVIG (n)	Rituximab (n)	Cyclophosphamide (n)	Other[a] (n)
Old (23)	17.19	3.04	57	43	10	13	15	0	2	7
New (15)	17.07	3.14	71	29	12	3	15	11	4	2

Abbreviations: ACTH, corticotropin; IVIG, intravenous immunoglobulin.
[a]Other immunosuppressive medications included azathioprine, mycophenolate, bolus dexamethasone, and autologous bone marrow transplant.

Mitchell et al., 2015 ***J Child Neurology*** 30; 976-82



Dale et al., 2014 ***Neurology*** 83; 142-50

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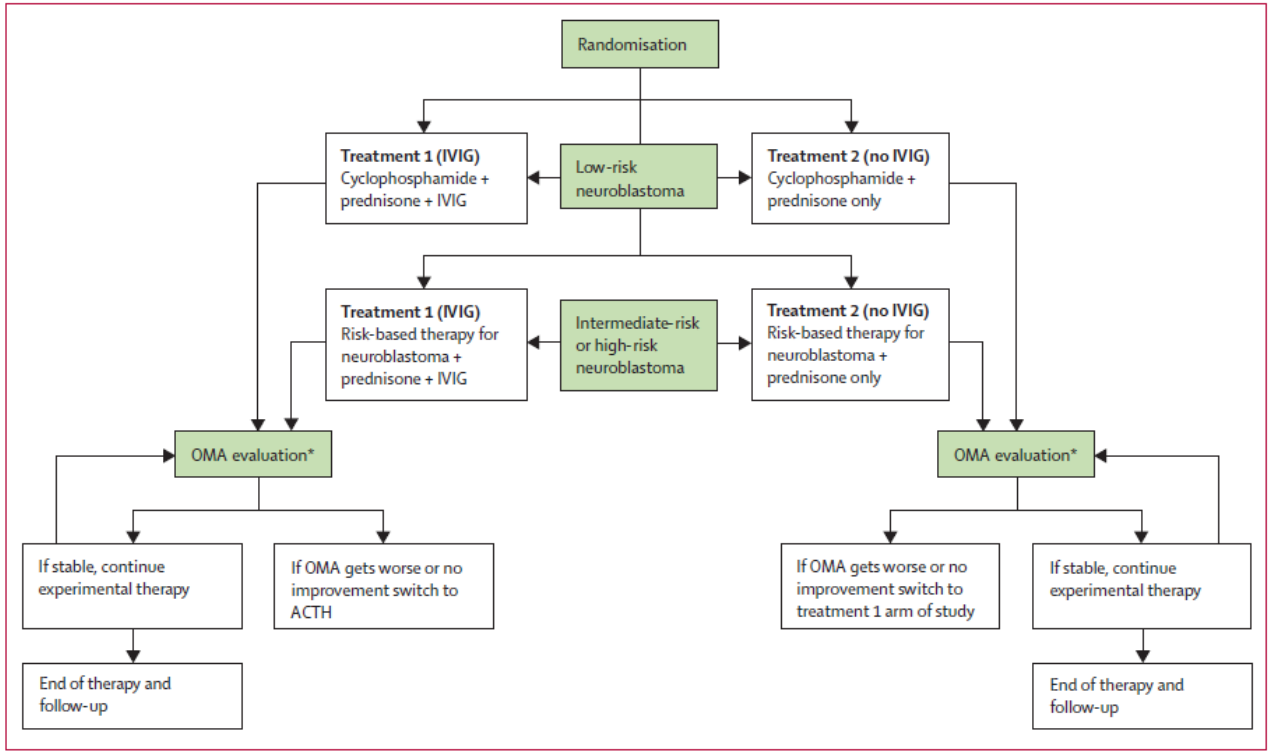
Relapses are bad for cognitive outcome

Multivariable linear regression model including 34 participants number of relapses occurring before neuropsychological testing ($p<0.001$) and OMS severity score at last follow-up ($p<0.001$) predicted FSIQ (adjusted R^2 =0.64).

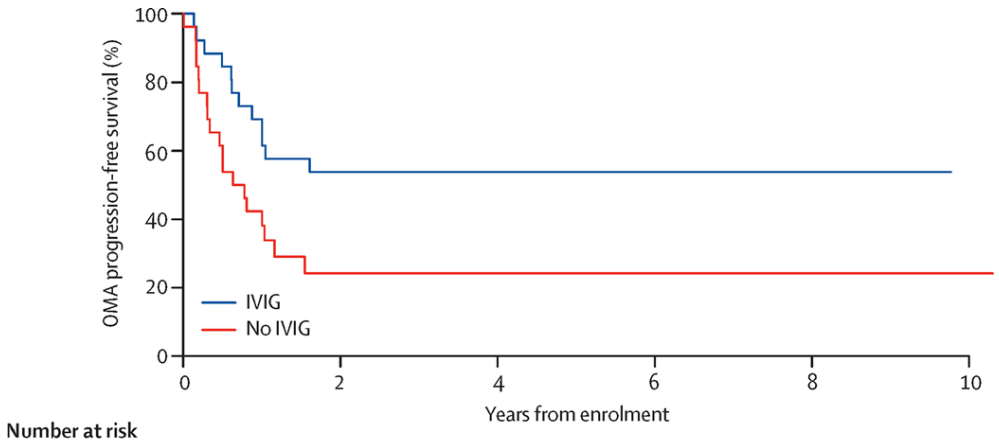
There was a mean decrease of 2.4 FSIQ points per OMS relapse

Sheridan et al., 2020 ***Dev Med Child Neurol*** 62(12):1444-1449

Intravenous immunoglobulin with prednisone and risk-adapted chemotherapy for children with opsoclonus myoclonus ataxia syndrome associated with neuroblastoma (ANBL00P3): a randomised, open-label, phase 3 trial



Patients randomized to receive IVIG received 1 gm/kg on day 0 and 1 of cycle one; day 0 of cycles 2 to 6; and then on day 0 of cycles 8, 10 and 12.



Number at risk (censored)						
IVIG	26 (1)	13 (2)	11 (3)	8 (5)	3 (3)	
No IVIG	27 (3)	5 (1)	4 (0)	4 (1)	3 (1)	2 (2)

De Alarcon et al., 2018
Lancet Child Adolesc Health 2(1); 25-34

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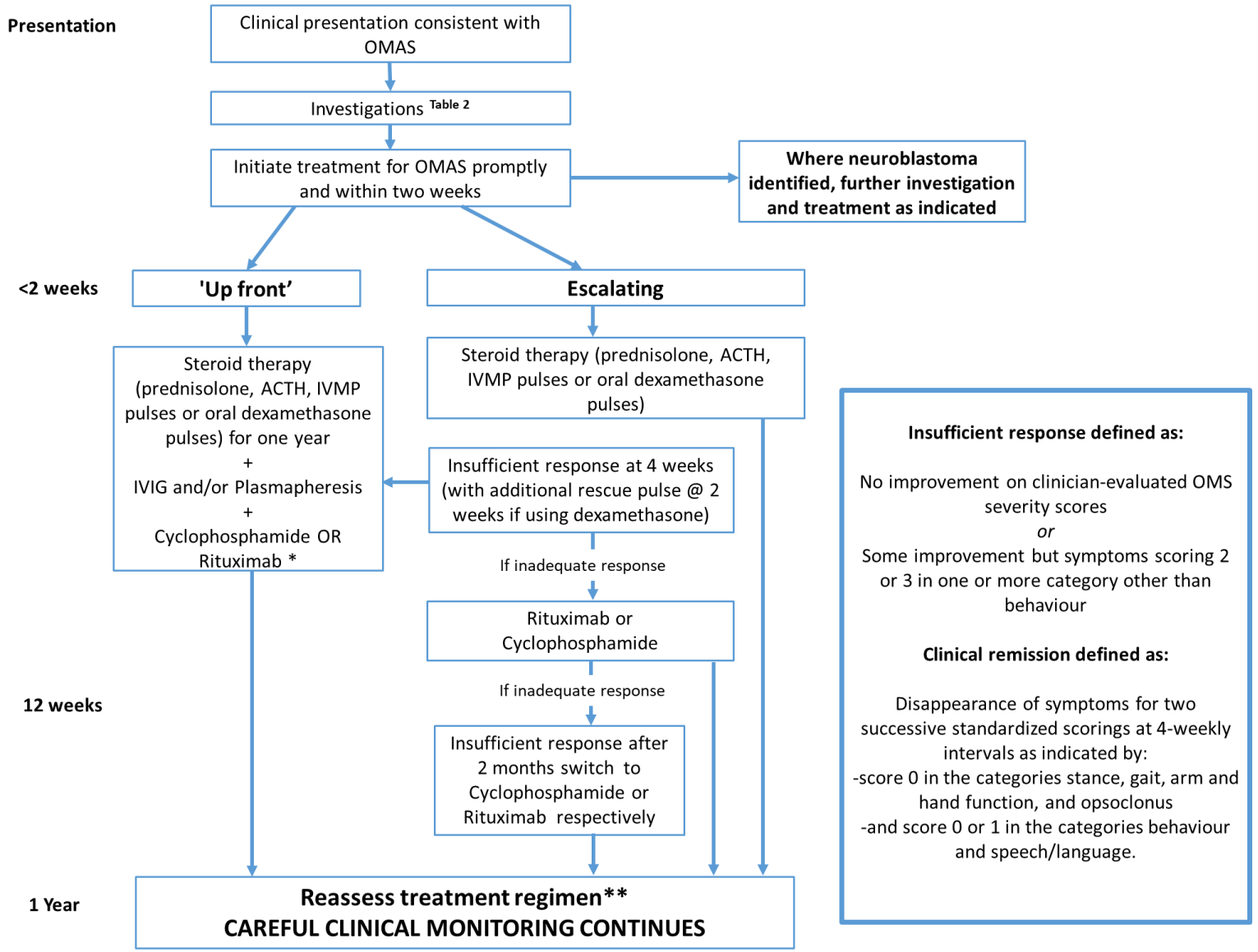
Presentation
Clinical presentation consistent with OMAS
Investigations Table 2
Initiate treatment for OMAS promptly and within two weeks
Where neuroblastoma identified, further investigation and treatment as indicated
<2 weeks
'Up front'
Escalating
Steroid therapy (prednisolone, ACTH, IVMP pulses or oral dexamethasone pulses) for one year
+
IVIG and/or Plasmapheresis
+
Cyclophosphamide OR Rituximab *
Steroid therapy (prednisolone, ACTH, IVMP pulses or oral dexamethasone pulses)
Insufficient response at 4 weeks (with additional rescue pulse @ 2 weeks if using dexamethasone)
If inadequate response
Rituximab or Cyclophosphamide
If inadequate response
Insufficient response after 2 months switch to Cyclophosphamide or Rituximab respectively
12 weeks
1 Year
Reassess treatment regimen**
CAREFUL CLINICAL MONITORING CONTINUES
Insufficient response defined as:
No improvement on clinician-evaluated OMS severity scores
or
Some improvement but symptoms scoring 2 or 3 in one or more category other than behaviour
Clinical remission defined as:
Disappearance of symptoms for two successive standardized scorings at 4-weekly intervals as indicated by:
-score 0 in the categories stance, gait, arm and hand function, and opsoclonus
-and score 0 or 1 in the categories behaviour and speech/language.

Evaluating treatment response

Insufficient response: No improvement on clinician-evaluated OMS severity scores or Some improvement but symptoms scoring 2 or 3 in one or more category other than 'behaviour'. **NB: This should indicate a need for escalation of therapy if following an escalation regimen**.

Clinical remission may be defined as disappearance of symptoms for two successive standardized scorings at 4-weekly intervals as indicated by:
score 0 in the categories stance, gait, arm and hand function, and opsoclonus and score 0 or 1 in the category behaviour

Relapse/Recurrence: any recurrence of OMS symptoms or signs in a child who has been in clinical remission

Table 3 Recommendations for the Dosing and Monitoring of Immunotherapeutic Agents in the Treatment of OMAS: Steroid Treatment and IVIg

Treatment of OMS in children	
Prompt treatment is generally considered important and should be initiated when a diagnosis of OMS has been made. Brief delay for surgical removal of an associated neuroblastoma may be considered or initial doses of immunotherapy given before tumor resection if there is delay in surgery. There remains uncertainty as to the benefits of a regimen of escalation of treatment vs front-loading treatment. Some children will respond to steroid treatment alone and will therefore be overtreated by a front-loading regimen. However, delay in effective treatment may be associated with a poorer disease outcome. If an escalation regimen is used, aggressive escalation may be required in cases with a poor response to initial treatment.	
Steroid treatment	
Regimen	Various regimens have been used including pulsed dexamethasone, adrenocorticoptropic hormone (ACTH), and methylprednisolone followed by prednisolone. Pulsed dexamethasone has been widely used as first-line steroid treatment. This may be given as: ➢ 20 mg/m^2/day in 2 divided doses on 3 consecutive days (3 d-treatment defined as 1 pulse) ➢ 12 pulses at 3 to 4 weekly intervals ➢ The scheduled 12 pulses of dexamethasone should always be completed, even with earlier complete remission. ➢ Additional dexamethasone pulses may be given, or the interval between the scheduled dexamethasone pulses may be shortened in patients showing insufficient response or improvement after dexamethasone but worsening of symptoms before the scheduled date of the next dexamethasone pulse. ACTH may be given as: ➢ 75 iu/m^2 intramuscularly twice daily for 1 wk, once daily for 1 week, alternate days for 2 wk, and then a gradual wean over 11 mo, but a slower titration from daily to alternate day treatment is often needed. Alternative corticosteroid regimens include: ➢ IV pulse methylprednisolone (30 mg/kg/d for 3–5 d) ➢ Pulse repeated monthly for 6–12 mo or followed by oral prednisone or prednisolone (starting dose 1–2 mg/kg/d) ➢ Weaning may be performed over 12 mo, which may be more rapid with steroid-sparing agent. Longer treatment may be needed.
Side effects	Potential side effects include irritability, hypertension, hyperglycemia, weight gain infections, and osteopenia, which may be lessened by using pulse rather than daily steroids.
Safety monitoring	➢ H2 blockers and/or antacids are recommended as prophylaxis for gastritis during steroid administration according to standard local procedures. ➢ Blood pressure, blood or urine glucose, full blood cell count, and blood electrolytes should be monitored by standard local procedures as clinically indicated. ➢ Patients on chronic corticosteroids should receive adjunctive treatment for bone health (calcium and vitamin D) with consideration of Dual-energy X-ray absorptiometry scan if on steroids for more than 6 mo, and *Pneumocystis* prophylaxis (trimethoprim-sulfamethoxazole), particularly if also had received other immunotherapy.
IVIg	
Regimen	May be given as: 2 g/kg over 2–5 d followed by 1–2 g/kg every 4 wk for up to 12 mo
Side effects	Potential side effects of IVIg include allergic reactions, thrombosis, headaches, and aseptic meningitis.

Abbreviations: IVIg = IV immunoglobulin; OMAS = opsoclonus-myoclonus-ataxia syndrome; OMS = opsoclonus-myoclonus syndrome.

Table 5 Recommendations for the Dosing and Monitoring of Immunotherapeutic Agents in the Treatment of OMAS: Rituximab

Rituximab	
Regimen	Used as upfront treatment and if an escalation regime is used, rituximab should be considered in the case of insufficient response (see monitoring) to steroids and/or cyclophosphamide. ➢ Rituximab regimes vary between centers with no evidence of superiority and include: ➢ Rituximab given as 375 mg/m^2/dose for 4 weekly doses ➢ Rituximab given as 500 mg/m^2/dose for 2 doses 10–14 d apart ➢ Rituximab given as 750 mg/m^2/dose for 2 doses 14 d apart
Side effects	Potential side effects of rituximab include allergic and infusion reactions, infections, and chronic hypogammaglobulinemia.
Safety monitoring	➢ Patients should be premedicated with a corticosteroid and an antihistamine. This can be dexamethasone 10 mg/m^2 IV before each rituximab infusion. This represents the morning dose of dexamethasone and therefore half the daily dose. ➢ Alternative steroid options include hydrocortisone and prednisolone ➢ Blood pressure, pulse, and body temperature should be monitored at regular intervals. ➢ In case of severe infusion-related reactions, the infusion should be immediately stopped and appropriate treatment initiated. Whether to resume rituximab treatment after rituximab-related reactions has to be decided by the treating physician, taking into account the severity of the reaction. ➢ All children should be hepatitis screened before commencing rituximab. Hepatitis B surface antigen, anti-Hep core antibodies for Hep B, plus Hepatitis C serology should be checked. The timing of this is to be as per local practice, but may need to be initiated if not responding at the time of the third dose of cyclophosphamide. ➢ Generally, serum immunoglobulins and lymphocyte subsets are monitored periodically to assess ongoing effects of rituximab. Blood counts and blood chemistries are monitored on a clinical basis. ➢ Prophylaxis for *Pneumocystis* using trimethoprim-sulfamethoxazole or others (according to local guidelines) and antifungal prophylaxis (according to local guidelines) are recommended for all children on rituximab and until 4–6 mo after rituximab treatment, although regional practice varies. ➢ If the patient has contact with individuals with varicella or measles, urgent contact with the medical team is recommended, and, if appropriate, prophylactic measures according to local pediatric oncology guidelines are recommended. ➢ In case of increased infection rate, consider administering IV immunoglobulin (e.g., 0.5 g/kg) irrespective of measured IgG levels. ➢ For patients with treatment escalation to rituximab, vaccinations may not be effective as long as B lymphocytes are decreased. After the end of immunosuppressive treatment, investigation of antibodies against vaccines or reimmunization may be considered according to local guidelines.

Abbreviation: OMAS = opsoclonus-myoclonus-ataxia syndrome.

Table 6 Recommendations for the Dosing and Monitoring of Immunotherapeutic Agents in the Treatment of OMAS: Cyclophosphamide

Cyclophosphamide	
Regimen	If not front-loading treatment, escalation to introduce cyclophosphamide should be considered if response to steroids is insufficient (see monitoring). ➢ Dosing regimens vary between centers, with regimens including: ➢ 25 mg/kg for patients <10 kg; 750 mg/m^2 for patients ≥10 kg ➢ Or: 500 mg/m^2 then escalation according to tolerance ➢ Administered IV at 4 weekly intervals until 6 doses have been given (or 3 doses if treatment is escalated to rituximab)
Side effects	Potential side effects of cyclophosphamide include nausea, vomiting, hair loss, infections, hemorrhagic cystitis, infertility, and secondary malignancy, although the more serious of these are uncommon with the above dosing regimen.
Safety monitoring	➢ Baseline renal function (creatinine) should be checked before each cyclophosphamide infusion ➢ Hydration and cystitis prophylaxis with Uromitexan (Mesna) may be given according to local guidelines. IV hydration is optional, but should be considered when oral hydration is inadequate ➢ Urine for erythrocytes may be monitored on the day of administration ➢ Pneumocystis prophylaxis using trimethoprim-sulfamethoxazole or others (according local guidelines) is recommended for children on cyclophosphamide and for a minimum of 3 mo after the end of treatment (or as per local guidelines). ➢ Precautionary measures for children at risk of varicella or measles apply according to local practice including advice about urgent contact with the relevant hospital team where there is exposure and, if necessary, prophylactic measures according to local pediatric oncology guidelines.

Abbreviations: OMAS = opsoclonus-myoclonus-ataxia syndrome; OMS = opsoclonus-myoclonus syndrome.

Table 7 Recommendations for the Monitoring of Children With OMAS

Monitoring in children with OMAS	
OMS scoring	**The Mitchell-Pike OMS rating scale defines symptoms severity on an ordinal scale of 0–3 in each of 6 domains (stance, gait, arm/hand function, opsoclonus, mood/behavior, and speech). Scores within this scale allow identification of clinical progress and should be assessed every 4 wk during treatment:**
Assessments	➢ All children with a history of OMAS, including those who responded well and are in remission, should be followed up at least yearly. ➢ Ophthalmologic assessment should be obtained at presentation and at age 5 y to exclude cataracts. ➢ Safety monitoring in immune treatment is described in the treatment text box.
At relapse	For patients without previously identified neuroblastoma: Repeat laboratory and biological studies (as described in investigations) including serum, CSF studies if clinically indicated, urinary catecholamine metabolites, and repeat imaging to exclude neuroblastoma.
	For patients with previously identified neuroblastoma: Imaging studies according to tumor localization to rule out relapse of neuroblastoma.
Cognitive	OMAS is associated with cognitive difficulties that may progress despite clinical remission of disease. ➢ All children with OMAS should be followed up to detect cognitive sequelae with special attention to ataxia, language development, attention, executive function, and behavior and sleep dysregulation. ➢ All children with OMAS should undergo a formal neurocognitive assessment to identify difficulties and provide early support within an education setting.
Assessment tools	To include both functional and quality of life assessments, including (but not exclusively): ➢ Cognitive testing: Bayley III, Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and Wechsler Intelligence Scale for Children (WISC) depending on age ➢ Behavior, attention and emotion: Child Behavior Checklist (CBCL) ➢ Social behavior and autistic traits: Social Responsiveness Scale (SRS)

Abbreviations: OMAS = opsoclonus-myoclonus-ataxia syndrome; OMS = opsoclonus-myoclonus syndrome.

NB: Long term sequelae of NB and treatment such as hearing loss, renal, infertility and secondary malignancies

Vaccinations in children with OMS

- The risk of reactivation of OMAS symptoms due to non-specific immune stimulation by vaccination
- The risk of preventable illnesses
- The ability of patients to mount an immune response after OMAS treatment.

Summary of consensus

- Early and timely initiation of diagnosis is important
- Clinical severity scales are important to help evaluate and monitor OMAS
- Investigations are important but biomarkers still do not have an established role in management
- Initiation of treatment to establish disease remission and prevent relapses is crucial in treatment
- Children with OMAS must have long-term follow-up

Many things we still do not know

- Specific biomarker to aid timely diagnosis
- Optimal pathway for relapsing patients and those refractory to current 2nd line treatment
- Outcome in very young patients
- Late cognitive decline in patients who have made full neurological recovery

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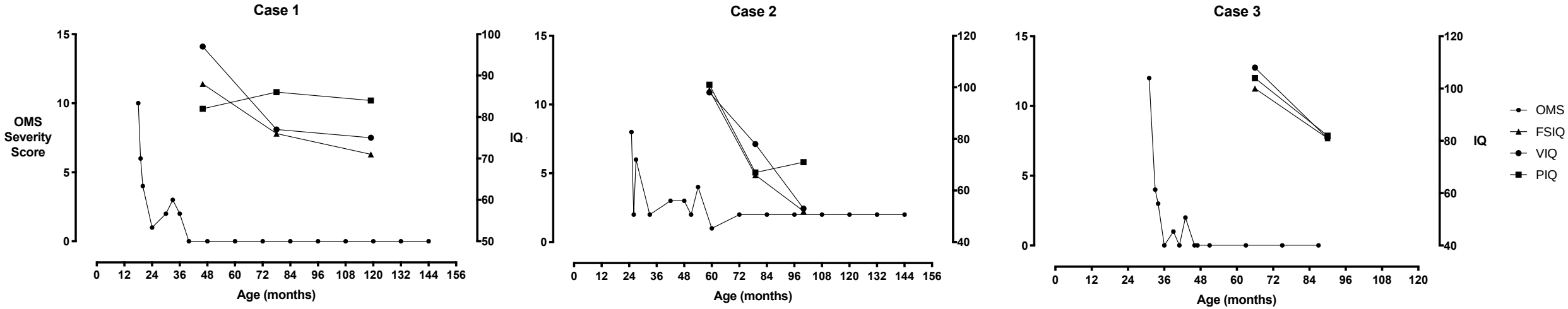
Evolving Cognitive Dysfunction in Children with Neurologically Stable Opsoclonus-Myoclonus Syndrome



Case	Gender	Age at Onset	Age at Diagnosis	Clinical Features at Presentation	OMS Score at Diagnosis	Presence of Neuroblastoma	Treatment	Response	Age at Last Follow-Up
1	Male	23 months	25 months	Unsteady gait, abnormal eye movements, opsoclonus, titubation, intention tremor and ataxia	8/15	No	Prednisolone IVIG	Good	13 years
2	Female	30 months	34 months	Unsteady gait, vomiting, opsoclonus and regression in language	12/15	No	Dexamethasone	Good	7 years 6 months
3	Female	17 months	17 months	Limb tremors, ataxia, loss of lower limb and truncal control and loss of speech	11/15	Yes	Surgical resection of neuroblastoma Dexamethasone Cyclophosphamide	Good	7 years 8 months

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