Summary of the Tenth International Workshop on Opsoclonus Myoclonus Syndrome Clinical and Basic Science Abingdon, UK 6-8th November 2022

SESSION 1: Updates, progress, and initiatives

i. OMAS History with tribute to Michael Pranzatelli: Wendy Mitchell

Iain Grummitt warmly welcomed everyone to the 10th International Workshop on Opsoclonus Myoclonus Syndrome supported by the DESST and OMSLife. All attendees introduced themselves. Ming Lim welcomed everyone and reminded everyone about care in needing to maintain non-dissemination of unpublished data.

Wendy Mitchell gave an overview of the history of the symposium all the way back to 2001 when the first DES workshop was done. Dr Beverley and Jane Stanton-Roberts were instrumental in the first meeting organisation. She mentioned that Mike Pike from Oxford was initially leading with a video of OMAS/DES child and the first 2001 meeting was attended by 17 UK speakers, 5 US speakers and 1 from EU. Subsequent meetings occurred in 2003, 2005, 2008, 2010, 2012, 2014, 2016 and 2018 with more patient group participation. She reminded us that Jocelyn Murphy who joined in 2008 was instrumental in writing parents/teacher/therapist guides. Ian Grummitt joined the steering committee from 2018. She reviewed some of the landmarks as below:

- B cells and cytokines in CSF (Rituximab proposed then)
- COG randomized clinical trial
- European clinical trial and database
- OMSLife database, NORD sponsorship
- Pavlov grants for neuroblastoma for OMAS
- Long awaited consensus paper published in 2022
- POOMAS international database since 2019.

Wendy Mitchell discussed some of the challenges remaining in the OMAS field:

- No surrogate biomarker of antigen/antibody in OMAS as of yet
- Lack of consensus for initial treatment, best relapse treatment and treatment of refractory OMAS.
- How to improve cognitive outcomes and prevent learning disabilities
- Late sequelae including anxiety disorders and other psychiatric problems
- Ongoing specialty care for adults who are OMAS survivors from childhood

Wendy Mitchell gave an overview of the life of the late Dr Mike Pranzatelli, who had spent most of his career dedicated to the study of OMAS. He sadly passed away in 2018 from pancreatic cancer. His background was one of a neuropharmacology fellow at CHLA from 1982-85, followed by moving to Columbia university in 1985 and then to the GW school of medicine, followed by moving to Southern Illinois University. His achievements included:

- First description of activated lymphocytes in CSF of children with active OMAS
- Reporting prevalence of CSF oligoclonal bands correlating with disease activity
- Describing the presence of a number of cytokines and chemokines in CSF of children with OMAS
- Introducing rituximab as a major component of OMS treatment
- Attempting to standardise aggressive first line treatment of OMAS
- Launching OMSUSA.org in 2001
- Publishing 152 manuscripts, with at least 53 written on OMAS.

ii. OMAS introduction and summary of last workshop - Ming Lim

Ming Lim provided an overview and a reminder of the last meeting in 2018 and also gave a tribute in memory of Dr John Wilson, Paediatric Neurologist who worked at Great Ormond Street Hospital, who recently died in 2020. In 2018, there was the launch of POOMAS (Paediatric Onset Opsoclonus Myoclonus Ataxia Syndrome Registry), the OMAS Consensus statement and Family education school pack, which has been translated since to 8 languages. He mentioned a clinical trial now underway in 8 countries, with 65 of the target 100 patients having been recruited. In addition, there was a reminder of importance of relapses on cognition in OMAS. He mentioned a pragmatic study of IVIG with prednisone and RIS adapted chemotherapy for children with OMAS associated with neuroblastoma (ANBL00P3) (de Alacron et al., 2008). He also discussed commissioning criteria for the use of therapeutic IVIg in NHS England.

Pavlov grants and immunobiology

- Autoantibodies to glutamate receptor delta 2 in OMAS (GRID2)
- Autoantigen discovery in OMAS – innovative MDT approach
- Cellular immunology of autoantibody-mediated encephalitides – relevance to OMAS
- Biomarkers and -omics

Ming Lim reminded us of the theme of OMAS through the life span and discussed the OMS patient registry, transition care (current lack of adult experts in the disease), emotional behavioural autonomic dysregulation (EAD) management in rare disease.

iii. OMAS Charter, membership and election: progress since last year - Ian Grummitt

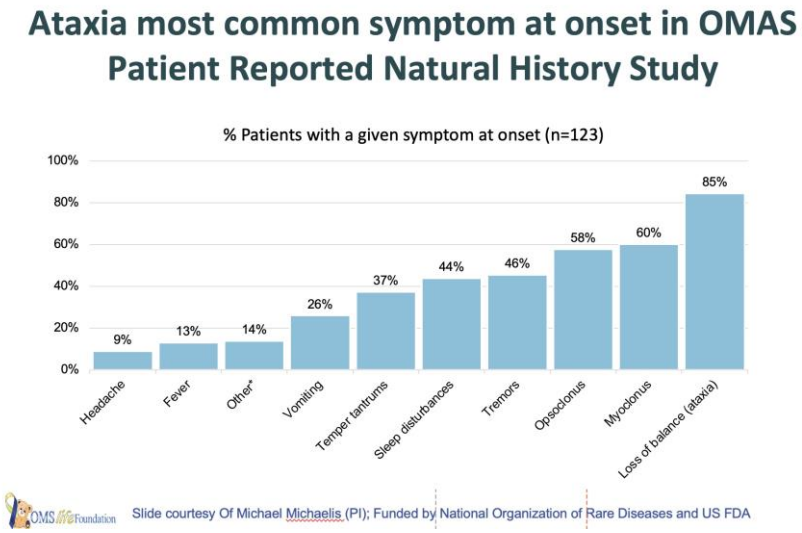
Ian Grummitt discussed that there were a few steering committee meetings post the 2018 meeting and that there were some changes to the charter – there was increase from 13 to 14 steering committee members. The current membership is 75; this is a mix of medics, researchers, 15 parents, and 3 allied professionals. Ian suggested that having new members of the committee which meets every 2 months virtually and any volunteers can approach any current member of the steering committee for this.

iv. OMAS: Consensus Statement - Ming Lim, Mark Gorman, Wendy Mitchell, Pedro de-Alarcon

This was recently published in Neurology-Neuroimmunology Neuroinflammation (Rossor et al., 2002). 47 physicians from 37 institutions and 12 parents/patients from OMS life and DES Trust. Ming explained consensus recommendations was structured as follows:

- Clinical evaluation
- Investigations
- Neuroblastoma treatment
- Immunotherapy
- Monitoring outcome
- Vaccination and re vaccination

Ming Lim reviewed he initial description by Kinsbourne in a series of 6 children with a myoclonic encephalopathy. The incidence is rare and UK incidence reported as 0.18 cases per million of the population. Most children tend to present before 5 yrs of age (mean age 18 months) and affects boys and girls equally with possible slight female preponderance. The diagnostic criteria were first mentioned in Genoa and reminded us of the need for 3 of 4 diagnostic features to be present.



Two scoring systems were discussed including the Mitchell and Pike OMAS rating scale (De Grandis et al., 2009) which is easier to use and more widely adopted compared to the OMS evaluation scale (Prantazelli et al).

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.

Tumours are associated with OMAS with peripheral neuroblastic tumours in 50% of children with OMS (most commonly neuroblastoma). OMS in 2-3% of neuroblastomas and presence/absence of tumour does not alter OMAS prognosis. Key is excluding other diagnosis. Results of recommendation for initial investigation of children with OMAS:

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.

He discussed neuroblastoma screening with urine catecholamines metabolites (VMA/HVA); spot urine is more practical than 24-hour collection. High resolution imaging is of upmost importance for diagnosis and monitoring. CT shows no evidence of inferiority to MRI but needs pre and post contrast imaging with significant radiation load. International neuroblastoma risk group stratification (courtsey of Dr Paolo Angelini)

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				NA	No		C Very low
	< 18				Yes		Q High
				Amp			R High

J Clin Oncol. 2009 27(2): 289–297

Treatment stratification dependent on risk. In terms of management he mentioned immunotherapy (no clear optimal treatment, front loaded vs stepwise escalation protocols), symptom management and monitoring. In the neuroimmunology world, early treatment and early escalation has been shown to be consistently beneficial with early and adequate immune therapies for improving outcomes. He discussed the average time to diagnosis was 11 weeks with worse outcomes seen if there is a delay of more than 2 months (Tate et al 2004, DeGrandis et al 2009).

Ming Lim also mentioned 2 treatment protocols: 1 is “front loaded” steroid therapy, IVIG and Cyclophosphamide/rituximab **vs escalation -** pulsed dexamethasone followed by 2nd line cyclophosphamide and then 3rd line to rituximab. He also reminded us of first paper by Kinsbourne, which included the use of ACTH as a potential alternative to steroids. The therapeutic window was discussed with what time course we should be intervening in, with compelling evidence that steroid treatment being crucial. Rituximab, if used and used earlier, also demonstrated better outcome in patients. Russel Dale published a paper, which showed improved outcomes in over 100 patients.

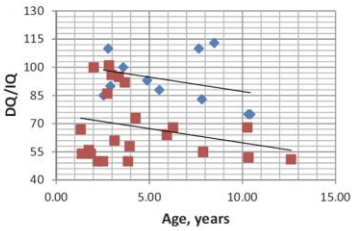
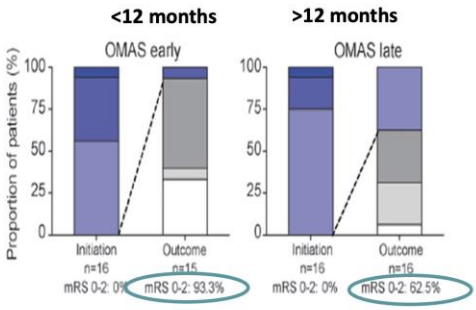


Table 3. Comparison of Treatment of the Old and New Groups.

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

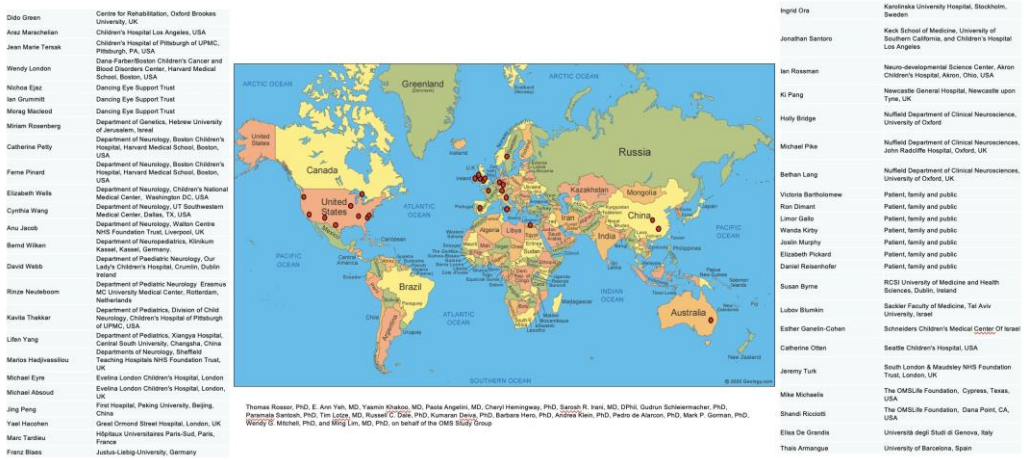
Abbreviations: ACTH, corticotropin; IVIG, intravenous immunoglobulin.
[a]Other immunosuppressive medications included azathioprine, mycophenolate, bolus dexamethasone, and autologous bone marrow transplant.

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



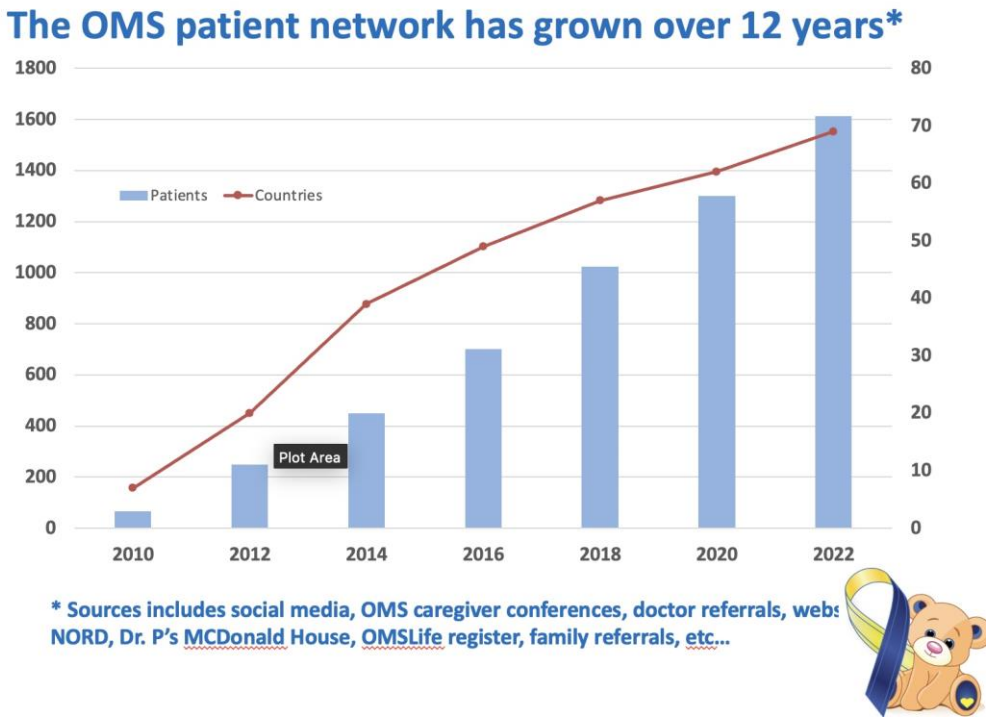
Dale et al., 2014 ***Neurology*** 83; 142-50

Sheridan et aL., in their 2020 paper, demonstrated the burden of relapses on cognition in terms of a mean decrease of 2.4 FSIQ points per OMAS relapse. In the consensus paper, there was a discussion of 2 strategies – 'up front' and escalating approaches to management in a protocol. Evaluating treatment response was based on certain criteria. Safety monitoring was also discussed and potential long-term sequelae that need to be monitored for different organ systems. Ming Lim then discussed experience of vaccinations in children with OMAS including risk of reactivation of OMAS symptoms due to non-specific immune stimulation by vaccination and the risk of preventable illnesses. Ability of patients to mount immune response after OMAS treatment. Children should be vaccinated after an interval if able to mount an immune response and also to consider the environment and when to do this. The talk finished with a map of all countries involved with the registry and reporting cases.



v. OMAS Registry: Progress & initial discussion, NORD: Michael Michaelis

Michael Michaelis started by recapping 2014 workshop plan, which he attended. The median time to diagnosis of OMAS since then has gone down from months to days. He also mentioned social media's impact and the importance of caregiver persistence in this part. The recent consensus statement mentioned above could be a game changer in the field and Michael emphasised some changes are already happening on the ground– treatment redirection, initial treatment changed and/or consultation with OMAS specialists initiated quicker. Some examples were given of children in London, USA with OMAS and their patient journey. The caregiver playbook also was a crucial development with NORD information booklet and collaboration video produced. A publication repository is also being designed. There was also some discussion in 2014 regarding a plan of action for Latin America and a guide on adult OMAS. OMSLife Registry – potential to find hidden patients outside of specialist areas and a large untapped group of patients remaining. This would allow ramping up of surveys from specific questions. There has been a collaboration between trio health and BCH as well.



Two studies were discussed: i)Trio health, NORD and OMSLife collaboration 2019 – collecting data including demographic data as well. BCH Collaboration in 2022 soon to be published this coming fall; ii)Second study being put together – general data and information. Some of the data from Trio health study data was shown in terms of patient demographics, clinical phenotype, time to diagnosis, Mitchell-Pike OMAS severity and association of symptoms and involvement of therapies like SLT etc. He finished on new opportunities in 2022:

- Behavioural issues – a registry can help with gathering behavioural data e.g., sensory processing disorders (SPD). Occupational therapy solutions and role of this vs medications.
- Plan of action for Latin American and guide on adult OMAS management

vi. Multinational registry: Mark Gorman

Mark Gorman discussed the POOMAS registry and that this was first conceptualised at the 2016 OMAS international workshop, with ongoing funding from numerous sources. Several steering committee personnel were task force members, and this was increased in number. The aims of registry were to determine illness course, prognostic factors, and treatment efficacy in addition to creating a registry of biological and imaging data in children with OMAS. The study design is longitudinal and observational natural history of consecutive visits. Study design has combination of retrospective and prospective patients and inclusion is for patients to meet Genoa criteria for formal diagnosis of OMAS and to be under 18 years of age. Initial case report form and follow up forms were shown. These focused on variations in disease course, prognostic factors and efficacy of treatment. Progress of this was discussed – team developed research protocol, CRFs, RED Cap database and have had IRB approval at BCH with 72 patients enrolled there already, and whole network has now reached 145 patients recruited with a target of 400 to be recruited. Seven other centres are enrolling participants. European centres also being activated now. The pace of enrolment shown including the challenges of participating during the COVID-19 pandemic. At present, they are currently enrolling 5 patients a month and hoping to accelerate this also. Some preliminary results on 86 patients were shown by Mark Gorman with summary of results: 53 female, median age of onset 26.7 months, disease duration 4.9 yrs; 35 of which were prospective patients. Tumour was detected in 51 patients with multiphasic course in 43, monophasic in 39 and parental history of autoimmunity in 26 patients. The next step is to validate all data on 145 patients and to focus on relapses, severity and predictors of relapse rate. They will continue to expand the cohort at existing sites and potentially include additional sites and or even have virtual recruitment.

SESSION 2: Trials, studies and interventions

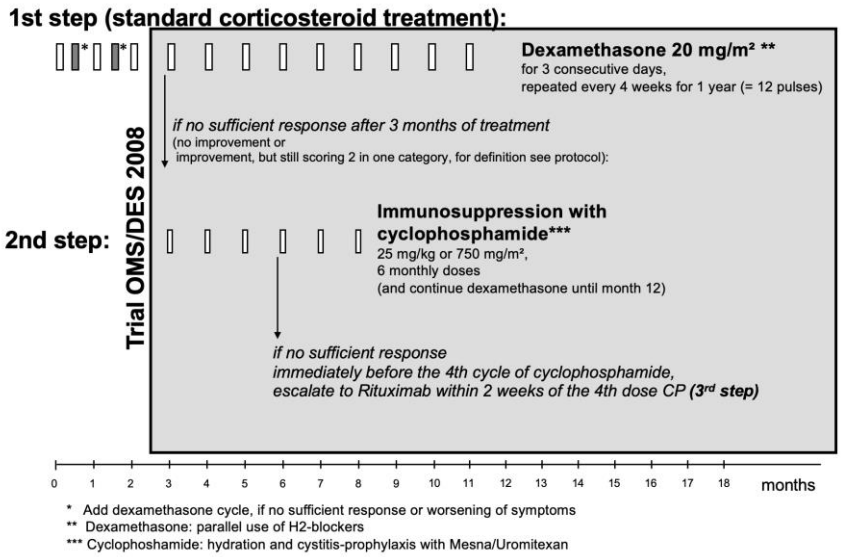
i. Completion of European Trial: Interim results - Gudrun Schleiermacher

Gudrun Schleiermacher started by reviewing the results of previous clinical trials. Biomarkers were discussed and a review of retrospective studies comparing neuroblastoma positive and negative OMAS children; results showed similar presentation and outcome overall for both groups. Schleiermacher reviewed that for randomised trials in Europe there is a need for international sponsorship.

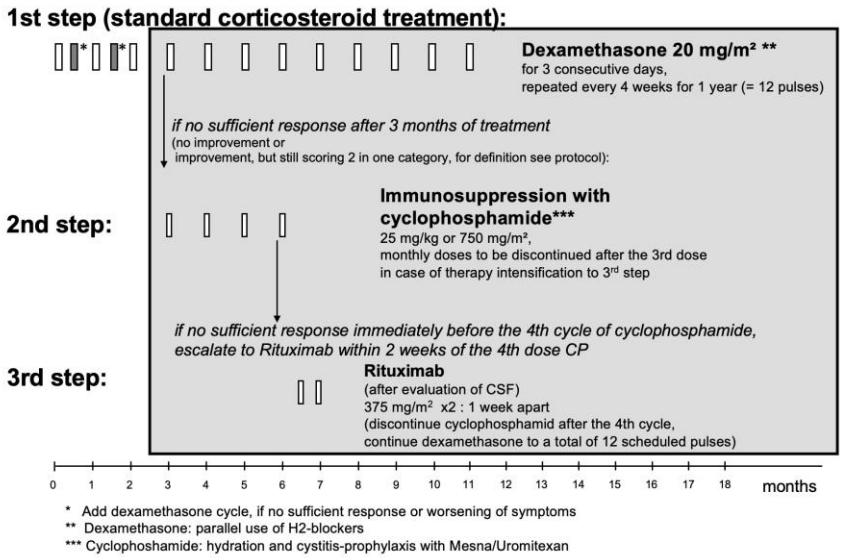
The aim of this trial was to evaluate prospectively treatment response in OMAS children with or without neuroblastoma, using a standardised OMAS scale and a standardised way of evaluating neurological and neuropsychological outcomes.

Eligibility criteria: OMAS patients with at least 3 of 4 diagnostic criteria – 6 months to 8 yrs eligible. Basic clinical info, biological samples and tumour samples, CSF and blood also needed. OMAS score given prior to therapy at given time points. Treatment schedule included dexamethasone boluses initially 20mg/m^2 for 3 consecutive days and repeated every 4 weeks for 1 year. 2nd line is cyclophosphamide 25mg/kg given in monthly doses (not high level as per chemo doses). If still no response – rituximab next step 375mg/m^2 (weekly for 2 weeks but could be extended to 4)

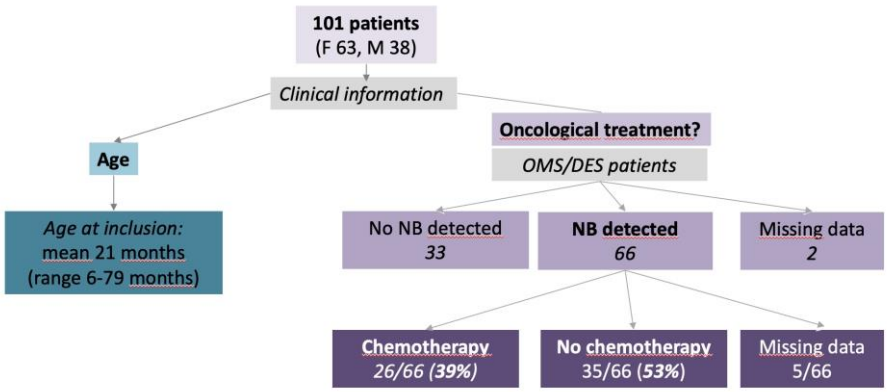
Treatment schedule *(first and second step)*

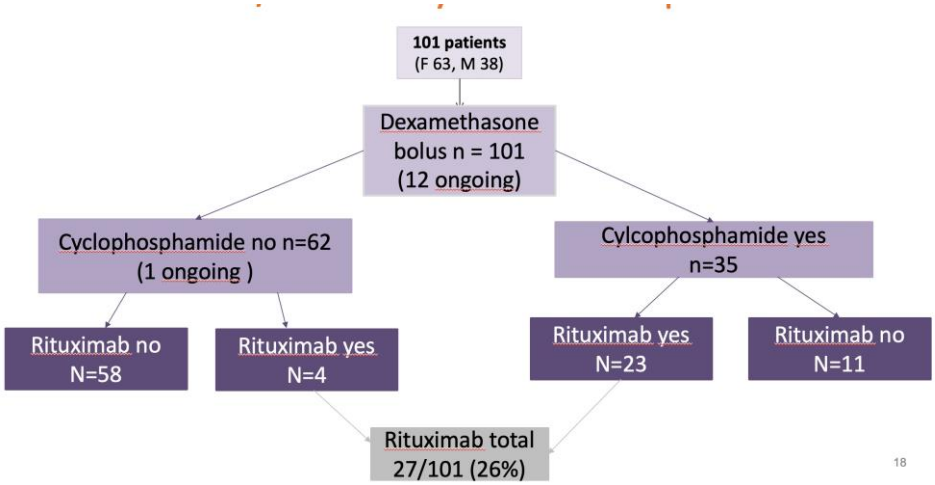


Treatment schedule *(third step)*



Preliminary Results: Enrolled patients so far as expected to date– end of enrolment in 2020. France, UK and Sweden were the biggest contributors in patient numbers. So far 101 patients included with slight predominance of female (63), mean age 21 months at diagnosis (6 months to 79 months). Neuroblastoma detected in 66 patients, of which 26/66 (39%) needed chemotherapy and 35/66 (52%) did not need chemotherapy. Neurological treatment: all 101 got dexamethasone boluses (12 ongoing still), of those 35 were escalated to cyclophosphamide of which 23 then had rituximab (and 11 did not). 62 patients did not have cyclophosphamide, of which 4 had rituximab later (without the cyclophosphamide step) and 58 did not receive it – this was a likely protocol deviation.

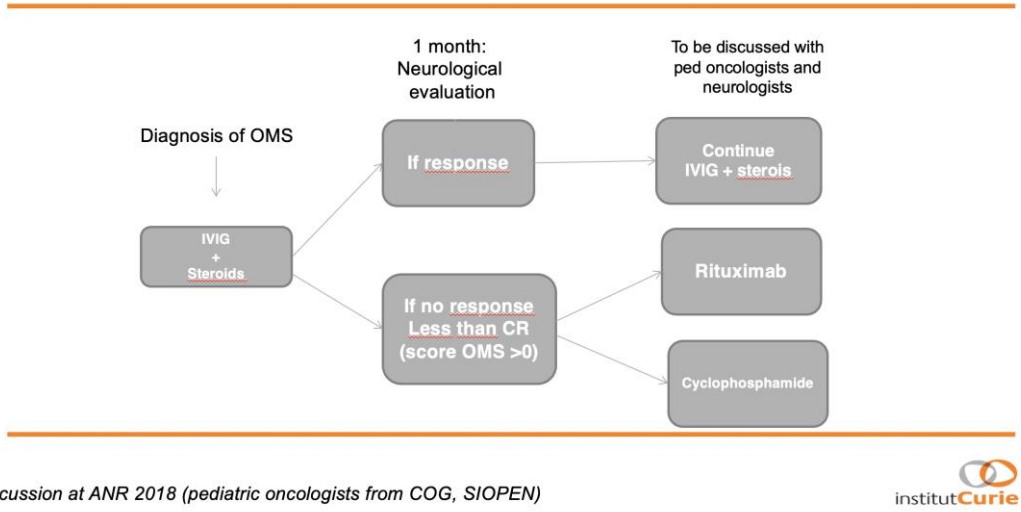




Serious adverse events were reported – no SUSARS and nothing that needed stopping the trial. In terms of data management, there is complete date for 62 out of 102 patients.

Challenges in treatment of OMAS and neuroblastoma discussed. Staging system mentioned from INSS to INRG SS. Genetic alterations in neuroblastoma have been looked at with distinct genomic copy number profiles – different prognoses depending on different mutations. Most recurrent mutations seen in ALK gene (8-10% of cases) – this may be important for targeted treatment as well in future although small % of patients (Ackerman et al 2018).

Different stratification systems: age, stage of disease, presence of symptoms and genetic alterations – SIOPEN/LINES – European low and intermediate risk neuroblastoma. When there are copy number alterations with segmental copy number alterations, this is associated with worse outcomes. Molecular characteristics of neuroblastoma (Brady et al Nat Comm 2020) are now becoming helpful in looking at the disease. Epigenetic features also now becoming more prominent in this field e.g., in neuroblastoma, importance of cellular identity and plasticity that arises from the observation that core regulatory circuits define 2 distinct cell states. Different cellular identities may be related to treatment response differences. In addition, the micro-environment of interest and single cell RNA sequencing has been looked at in mouse models of neuroblastoma and in humans. Circulating tumour DNA is relevant also given the need for biomarkers for this in the field. In neuroblastoma there are high quantities of cell DNA. So instead of repeated tumour biopsies it is possible to do blood samples to look at the ctDNA alterations. Future treatment protocols are likely to involve targeting epigenetics and genetic for stratification. There is currently an ongoing international retrospective observational study with the aim of describing characteristics of OMAS for patients with high-risk neuroblastoma; inclusion of patients at diagnosis under 21 yrs of age and a CRF is being circulated now.



Discussion at ANR 2018 (pediatric oncologists from COG, SIOPEN)

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Discussions of the presentation centred around the importance of registry work to pick up the higher risk of patients with breakthrough tumour cells and stage 4 cases. There was some discussion surrounding the high rate of chemotherapy 40% in this study relative to other centres.

ii. Proposal for International trial; Late cognitive and adaptive outcomes of patients with OMAS: A report from the children's oncology report - Perna Kaumar
This session was initiated by an in memoriam of Dr Audrey Evans and her contribution to the field with chemotherapy and radiotherapy use in solid cell tumours.

Perna Kaumar explained that many patients will have ongoing significant neurological deficit despite oncology treatment with COG protocol. ANBL00P3 study results discussed - 52 patients enrolled, of which 25 submitted evaluable neurocognitive data at diagnosis and at least within 2 years. Different scales used for neurocognitive and OMAS symptoms were rated by Mitchell-Pike scores. Neurological symptoms were evaluated as having complete, partial or no response or progressive disease. Of 25 patients 18 had moderate, 4 had severe, 2 mild. 16 had IVIG and chemotherapy; 9 were treated with chemotherapy only. Of 3 non-responders in IVIG+ 2 crossed to ACTH and 1 had stable disease.

When classifying treatment responders vs non responders: both groups showed stable adaptive functioning over time. For cognitive function, stable function over time as shown by mean scores over 2 years and mean change from baseline.
Non IVIG group showed slightly increased improvement in mean scores due to cross over. Perna concluded that IVIG+ group demonstrated greater improvement in adaptive development compared to chemo only group. Cognitive functioning and adaptive functional stable. Addition of IVIG to chemo appeared to have additional benefit but improved long term adaptive

Discussion post presentation centred around which cognitive tests should be used and whether a mean score of 80-85 is appropriate for a young child. There was also a discussion around challenges in cognitive assessments; some were lost to follow up and language barrier. There is a lack of neuropsychologists to perform these tests as well. Some discussion continued about the need for tests that reflect subtle differences in cognition and behaviour further down the line in the children's future. NIH toolbox was mentioned as being relevant to different conditions and can be administered remotely as well.

Perna Kaumar discussed in a follow up presentation that a number of publication have shown that early treatment is key in OMAS (Mitchell et al 2022; Russo et al 1997; Mitchel et all 2005).

She discussed that only a small number of studies have been published, of which most were based on retrospective datasets. Complete clinical trials include De Alacron et al and a Current multi-national European clinical trial first posted 2013

Current clinical questions:

- What can we do to increase benefit of therapy of those who don't respond?
- What is best strategy to follow and how can we treat symptoms long term?
- What are other EPD factors are contributing to the pathogenesis of OMAS?
- What is best way to coordinate necessary for a clinical trial?

There was a discussion around the next steps in terms of launching next prospective clinical trials:

1. Trial option 1 randomisation with 3 arms
    - Dexamethasone and IVIG
    - Cyclophosphamide vs rituximab
    - 3rd line escalation – adding next agent NOT received before

2. Trial option 2 with sequential escalation
    - Dexamethasone and IVIG at 4 weeks
    - Non-responders add rituximab and re-evaluate
    - Non-responders add cyclophosphamide and re-evaluate
    - Include IVIG?

3. Trial 3 intensification
    - Dexamethasone and IVIG re-evaluate at 4 weeks
    - Non responders add cyclophosphamide and rituximab

Funding is an issue and NCI/COG interested in a proposal, NINDS considering collaboration. There was a recommendation to create working group for this paper.

Discussion post presentation was centred around cyclophosphamide and the inclusion in this protocol proposal. Consensus was reached regarding using steroids (dexamethasone) initially. There was also discussion about different treatments and whether rituximab should be used up front or later on as 2nd/3rd line. Some discussion regarding rituximab and whether using aggressive treatment initially is important - how to know which ones are responders and which ones. Sustained hypogammaglobulinaemia as a possible side effect – may need long term IVIG. Suggested smaller group – for design of RCT with various professionals and parent representatives.

SESSION 3: Pablove grants session

i. **Detection of novel autoantibodies in children with OMAS - Thais Armangue**

Thais Armangue started by reminding us that in 1968 autoimmmune encephalitis was first described associated with tumours. Initial discovery was for intracellular antibodies, followed by seronegative antibodies in 2001 and then antibodies against neuronal surface antigens. She discussed that some of the antibodies discovered included NMDAR, mGluR5R, Dopamine 2R and neurexin-alfa. Thais reviewed the approaches to discovery of antibodies shown by screening, confirmation and then comparing to known antibodies. For unknown antigens, hippocampal neurons are often used followed by immunoprecipitation. Anti-NMDAR murine model antibodies that are pathogenic. However it is important to note not all treatment responsive immune mediated disorders are associated with antibodies (Dalmau et al, Ann Neuro 2007).

The JAMA neurology paper on clinical and immunological features of OMAS in era of neuronal cell surface Abs was discussed. She presented data on 114 adults with OMS – analysis for paraneoplastic OMAS, analysis of serum/CSF etc. and looking for Abs. Risk factors: encephalopathy and cranial nerve palsy were associated with OMAS. Further techniques to check for screening for Abs with new neuronal cell surface and intracellular OMAS. 13 had onco-neuronal/intracellular antibodies and 12 had neuronal surface Abs

Clinical risk factors for paraneoplastic OMS in adults

Table. Clinical Features of Patients With P-OMS and I-OMS

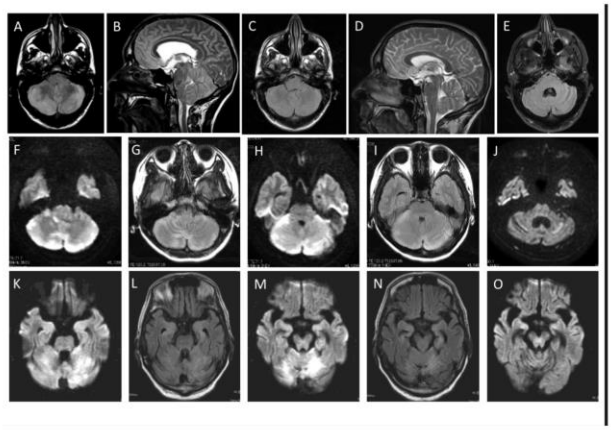
Characteristic	No. (%) P-OMS (n = 45)	I-OMS (n = 69)	*P* Value
Age, median (IQR), y	54 (45-65)[a]	38 (31-50)	<.001
Female	24 (53)	38 (55)	.86
Prodromal and/or infection	6 (13)	23 (33)	.02
Autoimmune background	3 (7)	11 (16)	.14
Presenting symptoms			
Acute vertigo	22 (49)	47 (68)	.04
Subacute ataxia or myoclonus	11 (24)	8 (12)	.07
Other symptoms[b]	12 (27)	14 (20)	.43
Additional symptoms at any time			
Encephalopathy	13 (29)	7 (10)	.01
Cranial nerve palsy	7 (16)	4 (5)	.02
Severe behavioral changes	6 (13)	4 (6)	.16
CSF studies (n = 90)	(n = 34)	(n = 56)	
Abnormal	24 (71)	42 (75)	.65
WBC count >5/μL	16 (47)	34 (61)	.21
Protein >45 mg/dL	14 (41)	18 (32)	.38
Follow-up, median (IQR), mo (n = 81)	(n = 38)	(n = 43)	
Duration, median (IQR), mo	14 (6-27)	20 (8-45)	.36
Poor outcome, mRS score >2[c]	23 (61)	7 (16)	<.001
OMS relapse	9 (24)	3 (7)	.04

Armangue et al. JAMA Neurol 2016;

In 45 children with OMS with or without neuroblastoma, 3 had anti-Hu Abs, 3 had non-specific and 3 had HGLY or HNK1 abs

GluK2, a new neuronal surface Ab in OMS and cerebellar involvement, was discussed with CBA testing in >600 patients showing 8 with GluK2 Ab only (7 cerebellar, 1 OMS, 5 cerebellitis), 6 had Gluk2, and concurrent antibodies (5 AMPA) and 1 NMDAR. Gluk2-Abs were suggested as pathogenic**.** Animal models for OMS were also discussed– learning from Ab mediated encephalitis. Thais showed some preliminary with data with intraventricular infusion of undiluted CSF from heathy individuals or intraventricular infusion with purified IgG from serum of children with Neuroblastoma positive OMS**.** In conclusion, young patients with teratoma can develop several forms of encephalitis without NMDA-R Abs amongst brainstem-cerebellar syndrome. Strong evidence supports OMS being Ab mediated.

GluK2-Ab can be found in OMS but also in cerebellitis



CBA testing >600 patients:

- 8 patients with GluK2-Ab only
  - 7 predominant cerebellar

  (1 OMS, 6 cerebellitis -> 2 edema compres IV v)
- 6 patients with GluK2-and concurrent Ab
  - 5 AMPAR, 1 NMDAR

Landa et al. Ann Neurol 2021;90:101-117

Discussion revolved around GluK2 and whether there an animal model using antibodies to GluK2? Thais explained as this is still in vitro, not yet shown in animal models. Also with regards to the paediatric OMS CSF donors for the study infusing this in mice, Thais explained a pool from 3 OMS paediatric patients were used, all with typical OMS. Thy tried to use the CSF from before immunotherapy.

ii. **Understanding OMAS immunity through study of its associated neuroblastoma - Miriam Rosenberg**

Quick review of NB and OMAS. A large cohort of OMAS NB tumours. NB+OMAS and NB-OMAS.

- Enrolled 53 patients in >10 years
- Collected tumour, CSF and bloods markers
- Tumour material from 38 patients – compared 38 NB+ OMAS vs 28 NB - OMAS
- Tumour analysis – RNAseq, genomic DNA, tumour histology
- CSF and bloods – autoantigen search and screen peptise libraries.

Key points discussed:

Shared epitope hypothesis mentioned – can we identify causative antigens from OMAS NB gene expression?

Gene expression in the tumour – looking at differential gene expression may help us find antigen. Markers of B and T cells – gene expression wise

RNAseq data – tumour immune classifier highlights differences in immune character of NB-OMAS.They ran as an algorithm and found that NB+OMAS very different to NB-OMAS.

High risk tumour had wound healing type of immune response (poor outcome – 50%), and OMAS had 50% IFN-gamma dominant immune response and C3 inflammatory immune response.

T cell and B cell signatures differ between OMAS and non-OMAS groups.
OMAS patients evaluated for severity of neuroimmune phenotype– stance/gait/arm and hand function/opsoclonus. 3 gene identified – NCAN, HTR6, ADRA2C. Good correlation between expression level and overall severity score

Distinctive OMAS associated tumour features

1. Enrichment of tertiary lymphoid structures with activated B and T cells
2. Significant lymphocytic infiltration that is DIVERSE – immune repertoires are diverse
3. HLA enrichment on non-canonical MHS Class II – were found

TLS in lung and liver cancer tumours are a positive prognostic indicator. Presence correlates with autoimmunity, autoreactive B cells.

T cell repertoire in tumours – more diverse in OMAS relative to Low Risk (LR) and High risk (HR)

Most OMAS specific T cell receptor – CASRDRREQFF. Heterogeneity of immune response in different OMAS patients.

MHC Class ii are enriched in OMAS patients compared to NB patients – HLA L alleles seen. HLADOB*01:01 – seen signal for this and related to B cells. Additional alleles seen were DRB1*01:01

Perspectives and current directions:

1. How are OMAS tumours different from non OMAS tumours in anti-tumour immunity?
    - Tertiary lymphoid structures
    - Formation of these structures happens in autoimmunity (B and T cell interactions) – seen in Rheumatoid arthritis – these could be driving the autoimmunity or cellular toxicity.
    - One way to look at is omaging mass cytometry – 40 or 50 different proteins being looked at same time. Quantitative and spatial information. Allows looking at immune cell markers

2. How are OMAS tumours/phenotypes different from each other? Heat map showed pattern of splicing in one subset of OMS patients.

Discussion revolved around check point inhibitors which are currently not been used or looked at. Also discussed innate immune cells – antigenic presenting cells shown in OMAS compared to non-OMAS NB.

iii. **Mapping somatic B cell responses - Dr Adam Handler**
B cells are key to the immunopathogenesis of many antibody-mediated disorders of the central nervous system (CNS). However, the mechanisms by which B cells escape central and peripheral tolerance checkpoints, become immunised against CNS autoantigens, and produce autoantibodies are incompletely understood. Work from our lab and others has identified heterogeneity in epitope binding with implications for mechanisms by which autoantibodies induce electrophysiological and behavioural effects *in vitro* and *in vivo*. In parallel with epitope heterogeneity, autoantibody production is driven by distinct populations of autoreactive B cells in different diseases, which suggests failure of tolerance checkpoints in CNS autoimmunity. Studies of lymphoid follicular structures has identified these as potential sites by which B cells escaping tolerance checkpoints can be immunised against CNS antigen with implications for the compartment-specific mechanisms of B cell immunotherapies. This talk will use examples to illustrate these areas of B cell immunobiology and relate these to antibody-mediated disorders of the CNS.

Conclusions mentioned included: Ab mediated disorders of CNS are a powerful mode to study B cell dynamics in autoimmunity. Autoantibody positivity can conceal underlying clonal heterogeneity in B cell responses that has mechanistic and functional implications. Autoantibodies can arise as a failure of central and peripheral tolerance mechanisms. **Deep cervical lymph nodes represent a key site of CNS antigen autoimmunisation.**

SESSION 4: New insights into immunobiology

i. Overview of immunobiology of OMAS: Jonathan Santoro
OMAS is an ostensible autoimmune disorder although the exact immunologic mechanisms remain unknown. This presentation will focus on the roles of B-cell, T-cell, and cytokine/chemokine signalling involvement in OMS and the molecular links to disease features, laboratory findings, and responses to immunotherapy. A focus on B-cell mediated recruitment to the CNS, maintenance of the B cell survival mice (via BAFF) and the role of T-cell regulation in acute attacks and relapses will be reviewed in addition to the role of cytokine/chemokine augmentation of disease.

Jonathan Santoro discussed that OMAS appears to be primarily driven through B-cell dysregulation although no definitive autoantibody has been identified. Promising target in GluK2. The role of T-cell activation of B-cells remains unclear. Cytokine and chemokine signaling, via B and T cell mediated mechanisms may be the activators of the potent immunogenic response in individuals who develop OMAS versus those that don't. Potential uses as biomarkers of disease activity/severity.

Genetic/inheritable modifiers may have a role in the development of abnormal immunologic signaling and cellular expansion.

ii. Antigen discovery in OMAS: new techniques for an old problem - Mark Gorman/ Tory Johnson/Michael Wilson

Mark Gorman started with a case of 21-month-old girl with ataxia and brief flittering eye movements 2 weeks after URTI – severe gait ataxia and was diagnosed with acute cerebellar ataxia. Typically most common cause of acute ataxia and diagnosis of exclusion. IVMP resulted in some improvement and then 2 further relapses. Further history showed slurred speech, tantrums positive family history of autoimmunity and exam showed irritability.

Mark Gorman highlighted the key challenges in OMAS work**.** Firstly clinically in distinguishing this from acute cerebral ataxia which happens as probably 42X the incidence based on a Dutch epidemiological study. Secondly, the elusive search for autoantibodies in OMAS

Mark Gorman explained PhiP-SEQ – Phase immunoprecipitation sequencing involving the entire human proteome, as means of antibody detection, citing ROHHAD syndrome – rapid onset obesity w hypothalamic dysregulation hypoventilation and autonomic dysfunction with neuroblastoma, as an exemplar (Benson et al Annals of neurology 2022). BCH OMAS samples have identified a few candidate putative targets which are currently being interrogated, including validation with CSF samples.

Tory Johnson talked about three NIH project goals to: i)prevent disease development, ii) provide answers to patients and iii) advance medical knowledge. A multimodal antigen discovery strategy was described utilising sera of patients with and without neuroblastoma and healthy controls

Summary: Although the diagnosis of OMAS can be made with confidence on clinical grounds alone when the classic symptoms are present, the diagnosis can be challenging for several reasons. It is much less common than its main mimic acute cerebellar ataxia. Not all patients present with all of the classic symptoms at onset or potentially ever. Only 50% of patients are found to have a neuroblastoma. These challenges can lead to delay in diagnosis and treatment. Identifying a definitive biomarker would significantly improve the diagnostic process. The OMAS Program at Boston Children's Hospital has partnered with the translational neuro-immunology research groups at UCSF and NIH to use novel techniques (such as PhIP-Seq) to interrogate patient samples for potential autoantibodies. Preliminary data was presented showing the presence of novel potential autoantibodies in a subset of patients with OMAS.

iii. New treatment horizons - Despina Eleftheriou

Key concepts discussed include:-

Effectiveness of some immunotherapeutic agents deemed of less potency, citing studies in ANCA associated vasculitis and childhood polyarteritis nodosa (MYPAN) demonstrating equivalence of MMF in efficacy compared to cyclophosphamide with superiority of safety and tolerance.

Measuring cumulative effect of treatment such as in corticosteroid toxicity using paediatric glucocorticoid toxicity index – composite pGTI

Roles of B cell lineage cells and respective immunotherapeutic targets in AI disease
Monoclonal Abs targeting CD19 or CD20 Rituximab, although sometimes studies have not revealed anticipated results such as Rituximab in SLE – Merril et al
EXPLORER phase II / III RCT – not licensed for SLE
BAFF – Belimumab in SLE
BTK inhibitors – Bruton's tyrosine kinase as target for AI diseases
Anti CD19 CAR cell therapies in SLE
IFN blockade – IFN gamma – emapalumab – genetic forms of HLH
JAK inhibitors – AGS
Anifrolumab in active SLE

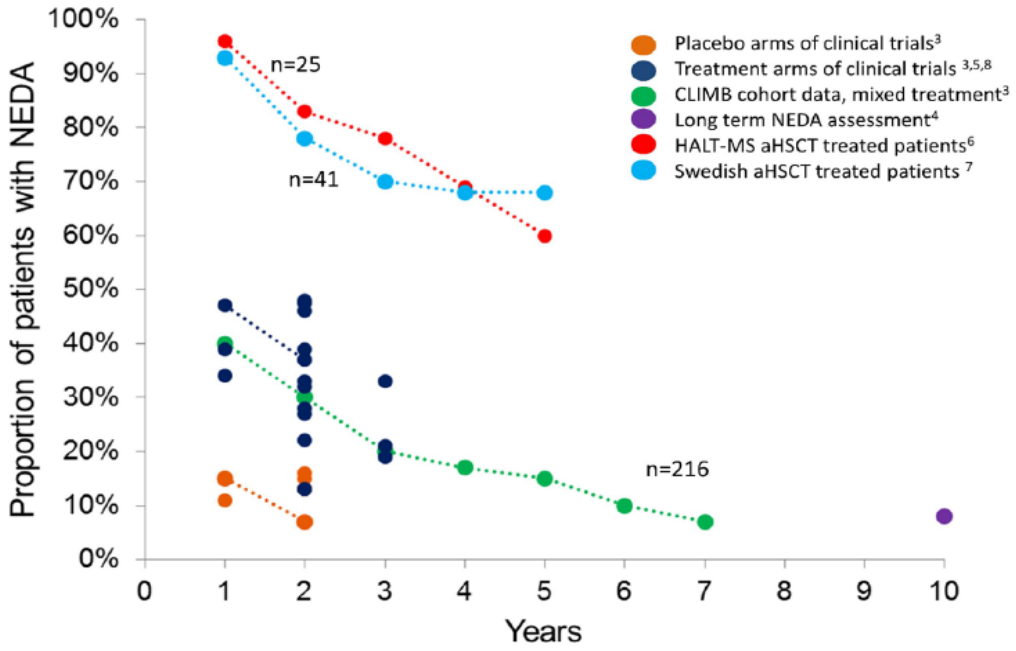
Summary: There are currently several novel immunomodulatory therapies emerging for the treatment of systemic and neuro inflammatory disorders. In this talk, Despina provided an update on current rationale for these treatments, mechanisms involved and stage of development. Ongoing challenges for conducting randomised trials of therapies in rare diseases and accessing novel therapeutics for routine clinical care was also discussed.

iv. High dose immunosuppressive therapy followed by HSCT in OMAS -Jennifer Clark
Jennifer Clark discussed HSCT for autoimmune disease, introducing the group to concept of allogenic (cells from another patient) or autologous (self). Toxicity and morbidity/mortality mentioned include GvsHD. Mobilisation of stem cells is often achieved using cyclophosphamide and filgrastim. High dose chemotherapy (conditioning regimen) causes in vivo ablation of T and B cell clones.
Use of ATG acts as in vivo T cell depletion. Post-transplant patients have a chance in effector cell population – with destruction of problematic clones.

The risk profile was then discussed:-

- Mortality rates less than 1%
- Infertility and secondary malignancy
- But also cumulative risk of treatments

Jennifer Clark discussed MS data for HSCT and its effectiveness:



Sormani et al, Multiple Sclerosis Journal 23:201-4,2017

Other disease examples of HSCT:

- Myasthenia Gravis discussed – 10-20% of patients treatment unresponsive
- CIDP
- Rasmussen's encephalitis

She discussed HSCT in OMAS - 1 case series (Johnston et al 2018):

- 10 month male INSS stage IVS neuroblastoma: 7 yrs from transplant no recurrent OMAS and mild cognitive and learning deficits
- 21 months old - auto-HCT - Transplant course complicated by Candida UTI and adenovirus reactivation and no significant improvement with HCT

She then introduced the concept of adjunct high dose immunosuppressive therapy (HDIT) in HCT; alongside refinements of mobilisation regimen; and prior CMV and EBV risk stratification to improve outcome of transplant.

Summary: Opsoclonus myoclonus ataxia syndrome is an autoimmune neurologic disease often associated with underlying malignancy or infection. Standard treatment strategies aim to modulate the immune system but patients with refractory disease suffer significant morbidity with long term neurocognitive sequelae. High dose immunosuppressive therapy (HDIT) with autologous hematopoietic cell transplantation (HCT) is emerging as a viable therapy for autoimmune neurologic diseases. This strategy allows dose intensification of immunosuppressive therapy and can result in a sustained immunomodulatory response. HDIT with HCT has been most studied in multiple sclerosis where patients with relapsing remitting disease that has been refractory to other therapies have as high as 69% 5 year event free survival. Recent recommendations by The National

Multiple Sclerosis Society include HDIT with auto HCT as standard therapy for select patients. There is data to suggest benefit of HDIT with auto HCT in other autoimmune neurologic diseases including myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, and Rasmussen's encephalitis. One published case series of HDIT with auto HCT for OMAS showed complete response in one of the two patients. HDIT with HCT has low associated risk for mortality or long term morbidity and is being studied in FHCRC protocol 2260 for numerous autoimmune diseases including OMAS.

Discussion centred around whether HSCT in OMAS should be used potentially as first line. Transplant associated microangiopathy (TMA) was mentioned as a risk for HSCT – seen in neuroblastoma patients in literature.

vi. Pavlov Grant updates: Naveen Visawanthia, Kerstin Lynam CEO

The next grant cycle of applications will open in May 2023 with Letters of intent to be submitted early July 2023. Successful projects from a scientific board review, will be invited for full application in August 2023.

The awards will comprise of 100k multiyear grants and will start with 50k and get renewed in subsequent years. Seed grant $50,000 initial but some flexibility and willing to work on a project deemed acceptable by scientific advisory committee Awards will predominantly be based on:-

- Scientific quality of application and secondarily on promoting applicants at early stage of career
- Hypothesis driven research with clear endpoint
- Clinical or basic science research

SESSION 5: Advanced imaging in neuro-inflammatory disorders

i. PET-MRI in neuro-inflammatory conditions: Paris experience with TSPO-PET applied to MS - Benedeta Bodini

Benedta Bodini spoke about the Paris experience of using PET imaging to explore neuroinflammation in multiple sclerosis. Given the involvement of both adaptive and innate immune systems in the pathobiology of neurodegeneration, PET is targeting neuroinflammation (Bodini et al 2021). She mentioned the challenge of low resolution imaging in addition to radiation dosage. There is now improved signal to noise ratio using second generation TSPO tracers allowing for quantification of PET images. The region of interest being analysed (TSPO binding in MS brain); results were shown in 37 MS patients.

ROI analysis of T1-SE lesions showed a subgroup that are highly active despite the dogma that these are dead areas. Three patients shown with secondary progressive MS showing level of chronically activated microglia varies massively between the 3 even though all clinically similar. 2% of total lesions active as per Gadolinium enhancing lesion and almost 40% shown to be active on DPA.

Data shown on dynamic evolution of DPA-714 subacute active lesions and discussion around the possible clinical relevance of this? The data showed that the number and proportion of active lesions correlated well with the clinical worsening of patients i.e. EDSS step change in 2 years. Unpublished data (Hamazaoui et al 2022) was also shown on exploring the smouldering component of MS lesions with a new PET-based classification system of: Active, mixed active/inactive and inactive lesions. Homogeneously active lesions were seen in 53% and mixed active/inactive in 6%. This was able to predict cortical atrophy over 2 years as well. Data was also presented showing choroid plexus in people with MS are larger than in healthy controls. Choroid plexus (CP) volume is in fact 35% greater in patients with MS compared with healthy controls. CP volume is correlated with parenchymal inflammation and higher DPA uptake by 20% almost compared to healthy controls (RRMS).

ii. Ultra-Highfield imaging in autoimmune encephalitis - David Carmichael and Michael Eyre

Routine (qualitative) brain imaging in OMS is typically normal in the acute phase. Recent advances in MRI enable quantification of basic MRI parameters to provide measurements which are sensitive to tissue microstructure and fluctuations in brain activity, enabling detection of more subtle changes associated with disease. Few such studies have been undertaken in OMS: Anand *et al.* reported cerebellar atrophy and thinning of motor and visual cortices in the chronic phase (Anand et al., 2015); Oh *et al.* reported increased PET glucose uptake in the cerebellar deep nuclei and increased MRI functional connectivity between the oculomotor and visual systems in a 22-year-old woman with acute OMS (Oh et al., 2017).

In this presentation David and Michael shared some examples of opportunities for new insights into paediatric neurological disorders afforded by advanced neuroimaging, including:

- Pilot work analysing longitudinal changes in brain structure on routine clinical neuroimaging in a cohort of children with autoimmune encephalitis (including 4 OMS patients)
- Advantages and challenges of ultra-high field (7 Tesla) MRI for imaging brain structure and function in children
- Overview of a currently ongoing project acquiring 3T and 7T multimodal imaging and cognitive data in children and young people with NMDA receptor antibody encephalitis.

They concluded that 7T imaging is now a usable whole-brain submillimetre technique. Increased signal to noise ratio at 7T brings opportunities including increased spatial resolution (insights into smaller structures, sensitivity to small changes) and increased power to detect metabolites with spectroscopy. There are opportunities for multimodal imaging in OMAS with localising neuropathology and relating back to molecular mechanisms, identifying sub-categories of patient and understanding sequelae and long-term symptoms.

SESSION 6: Neuro-behavioural aspect of OMS

i. Psychiatric manifestations of neuro-inflammatory conditions - Aaron Hauptman

Aaron started by talking about the challenge of neuropsychology in the field of OMAS. He mentioned different behavioural phenotypes. He also discussed psychiatric and neuro-psychiatric co morbidities and discussed that often there is a degree of overlay. Immunomodulatory therapy also involved in this aspect. Neuropsychiatric features of OMAS were reviewed including insomnia, irritability, rage attacks, frontal-executive dysfunction and mood and anxiety issues. Shared features with other neuroinflammatory disorders and features which are overall with cerebellar injuries. Some limbic involvement as well. Severe and consistent insomnia is also a feature of OMAS.

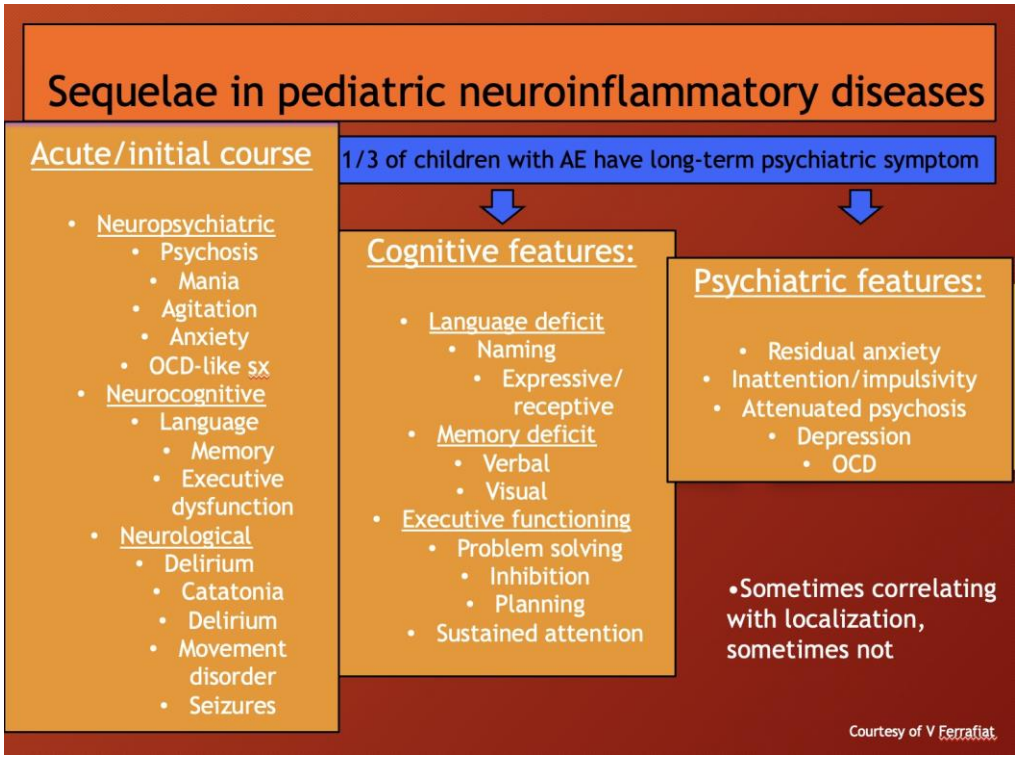


Figure showing sequelae in paediatric neuroinflammatory diseases.

There was a discussion and review of the literature of the concept of cerebellar cognitive and affective syndrome (CCAS), which is a new concept of 'dysmetria of thought'. CCAS involves executive function, visuo-spatial, personality/affect and even language. Studies show voxel-based morphometry shows extensive reduction in cerebellar grey matter in OMS. There was also mention of the role of the cerebellum in neurobehavioral symptoms.

Some cases were presented to demonstrate neuropsychological issues with OMAS and management techniques. Psychopharmacology in neuroinflammatory diseases was also discussed with disease modifying therapies and that modulating underlying

illness may halt or reverse psychiatric symptoms to varying degrees. Down syndrome and regression was also discussed with anti-TPO Ig elevated.

Modifiers of underlying pathophysiological circuity were discussed. Psychiatric agents have direct impact on illness state and may reduce likelihood of future illness. Protective effects of using psychiatric medications for bipolar, OCD etc. Symptom modifying agents were mentioned and behavioural therapies were also discussed briefly.

Discussion post talk revolved around psychiatric medication and timing of this within these conditions.

ii. Anxiety and OMAS

From the 2018 workshop we know that 1 in 10 of the normal paediatric population will have contact with mental health services, 20% of those who have chronic non-brain injury and 40% of those where the disease involves the brain. Rates of anxiety have been increased to such an extent to it now being the most common mental illness in the US. The COVID-19 pandemic led to a huge increase in anxiety and some insight into possible causes include:

- Decrease in face to face social contact
- Increase in social media interaction
- Lack of routine
- Poor sleep habits
- Decreased resilience

SESSION 7: Summary of the sessions – Ming Lim

Ming started with a tribute to Dr Pistoia with regards to his contribution to the field, who sadly passed away this year. He went on to summarise the main points of the meeting and discussed the main themes that came up during the course of the 3 days. He also discussed lessons to be learnt from research into other neuroimmunology diseases.

One of parents of OMAS patients made an important comment about feel for community with other parents and researchers seeing OMAS patients. Mark Gorman described the importance of perseverance, persistence and resilience in OMAS. Pedro concluded by thanking the parents and young investigators who attended.