Effect of relapses on neuropsychological outcome in a multinational study of 81 patients with pediatric opsoclonus myoclonus ataxia syndrome

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Background

- 1979 - first publication on cognitive sequelae after OMS
- Since then, mostly small retrospective studies using diverse methods published
- Cognitive sequelae reported in 50-90% of patients
- Profile of neurocognitive sequelae reported includes intellectual disability, as well as more specific deficits in attention, expressive language, visuospatial function and behavior

Background

- Limited data on risk factors which predict adverse cognitive outcome
- Potential risk factors for worse outcome
  - Younger age of onset
  - Severe presenting symptoms
  - Treatment delay
  - Relapsing course

Objectives

- Describe the neuropsychological profiles of a large multi-national cohort of children with OMS
- To determine predictors of intelligence quotient in the cohort

Methods

- Combined retrospective (looking backwards) and prospective (looking forwards) cohort (group) study of patients with OMS evaluated at one of three academic medical centers between 2006-2013
- Clinical and neuropsychological data obtained from medical records

Methods

- Standardized neuropsychological battery established in June 2012
- Patients tested prior to June 2012 were included in the neuropsychological analyses if they had prior testing at age >2.5 years of sufficient quality as determined by the site neuropsychologist

Key definitions

- Relapses: worsening of OMS symptoms lasting for at least 72 hours following a period of stability or improvement for at least 30 days, or the escalation of immunotherapy as a proxy measure
- Remission: score 0 in the categories stance, gait, arm and hand function, and opsoclonus, and score 0 or 1 in the category behavior for at least 30 days

Rationale for relapse definition

- Limited published studies have used range of duration of increased symptoms from 24-72 hours
- Study neurologists felt there were often brief increased symptoms of OMS that do not clearly represent a relapse; we therefore chose 72 hours

Rationale for relapse definition

- Ideally a quantitative scale with specific cutoff would be used to measure the “worsening” symptoms but this does not exist and would be difficult in this study setting (relying on medical records with varying detail)
- Similar general definition is used in other autoimmune neurological disorders such as multiple sclerosis

OMS Rating Scale

Table 1. Opsoclonus Myoclonus Syndrome Rating Scales.

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

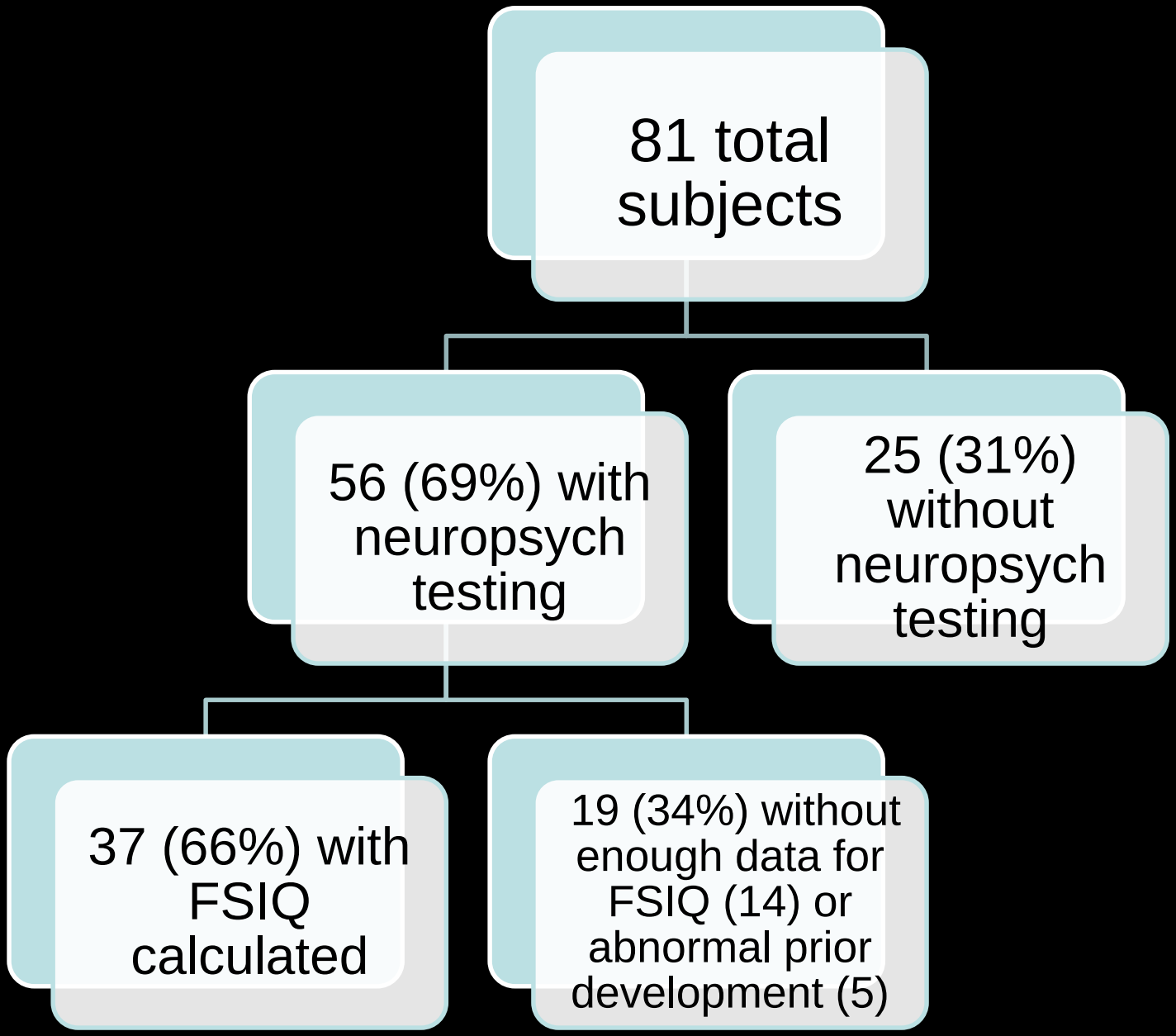
Mood/Behavior
- 0: normal
- 1: mild increase in irritability but consolable; and/or mild sleep disturbances
- 2: irritability and sleep disturbances interfering with child and family life
- 3: Persistent severe distress

Speech
- 0: normal for age, no loss
- 1: mildly unclear, plateaued in development
- 2: loss of some words or some grammatical constructs (ie, from sentences to phrases) but still communicates verbally
- 3: severe loss of verbal communication and speech.

Mitchell WG, et al. J Child Neurol 2014

Outcome measures

- Primary
  - Wechsler full scale intelligence quotient (FSIQ) at last available testing session
- Secondary (IQ subsets)
  - Verbal and nonverbal IQ
  - Processing speed and working memory indices


81 total subjects
56 (69%) with neuropsych testing
25 (31%) without neuropsych testing
37 (66%) with FSIQ calculated
19 (34%) without enough data for FSIQ (14) or abnormal prior development (5)

Characteristic	Overall (N=81)
Gender (N (%))	
Male	32 (39.5%)
Female	49 (60.5%)
Race (N (%))	
Unknown	11 (13.6%)
White	61 (75.3%)
Black or African American	2 (2.5%)
Asian	5 (6.2%)
Other	4 (4.9%)
First language (N (%))	
English	59 (72.8%)
Swiss	9 (11.1%)
German	2 (2.5%)
Spanish	2 (2.5%)
Other or unknown	9 (11.1%)

Current age (years)	
Mean +/- SD	11.68 +/- 5.57
Median (range)	11.49 (2.41-27.82)
Age of OMS onset (months)	
N	78
Mean +/- SD	20.84 +/- 12.95
Median (range)	18.81 (5.42-90.84)
OMS History (N(%))	
Unknown	6 (7.4%)
Monophasic	22 (27.2%)
Multiphasic	53 (65.4%)
OMS Severity at Presentation	
N	78
Mean +/- SD	10.2 +/- 3.3
Median (range)	10 (3-15)
OMS Score at last follow-up	
N	80
Mean	1.8 +/- 2.4
Median	1 (0-11)

Remission achieved	
Unknown	5 (6.2%)
No	30 (37.0%)
Yes	46 (56.8%)
Time from OMS onset to 1st remission (months)	
N	35
Mean +/- SD	9.06 +/- 8.21
Median (range)	7.00 (0.2-39.02)
Number of relapses per patient	
N	71
Mean +/- SD	2.73 +/- 3.02
Median	2 (0-10)
Duration of Follow-up (years)	
N	80
Mean +/- SD	6.98 +/- 5.15
Median (range)	5.65 (0.15-19.88)

Time between Onset & First Treatment (months)	
N	65
Mean +/- SD	2.64 +/- 3.32
Median (range)	2.01 (0.03-19.86)
Tumor (N (%))	
No	43 (53.1%)
Yes	38 (46.9%)
School Education	
Unknown	6 (7.4%)
Not of school age yet	14 (17.3%)
Mainstream school	16 (19.8%)
Mainstream school with formal support	30 (37.0%)
Special school	15 (18.5%)

Characteristic	Overall (N=50)
Age at Neuropsych Testing (years)	
N	50
Mean +/- SD	8.44 +/- 4.61
Median (range)	6.67 (2.58-20.92)
OMS Duration at Testing (years)	
N	50
Mean +/- SD	6.59 +/- 4.75
Median (range)	5.08 (0.40-19.87)
Full Scale Intelligence Quotient	
N	37
Mean +/- SD	84.38 +/- 20.55
Median (range)	90.00 (40-114)

Characteristic	Overall
Verbal IQ or Verbal Comprehension Index	
N	41
Mean +/- SD	88.24 +/- 17.00
Median (range)	91.00 (47-116)
Non-Verbal IQ or Perceptual Reasoning Index	
N	42
Mean +/- SD	83.83 +/- 17.96
Median (range)	85.00 (45-125)
Working Memory Index	
N	26
Mean +/- SD	82.35 +/- 15.30
Median (range)	80 (50-105)
Processing Speed Index	
N	33
Mean +/- SD	83.39 +/- 21.22
Median (range)	80 (50-122)

Comparison between IQ subtests

- Nonverbal IQ lower than verbal IQ by 4 points
- Trends towards lower processing speed and working memory compared to verbal IQ but not statistically significant

Potential predictors

- No relation between FSIQ and following potential predictors
  - Gender
  - Age of OMS onset
  - OMS severity at presentation
  - Time to first remission
  - Presence or absence of tumor
  - Time to first immunotherapy
- Thus, unable to predict low versus high risk groups with features available at OMS onset

Potential predictors

- FSIQ significantly lower with
  - Higher OMS severity score at last follow up
  - Higher number of relapses
  - Failure to achieve remission
  - Multiphasic (at least 1 relapse) compared to monophasic course

Why didn’t time to treatment affect IQ outcome?

Treatments received

TREATMENT	N (%)
Methylprednisolone	16 (19.8)
Prednisone / Prednisolone	50 (61.7)
Dexamethasone	21 (25.9)
ACTH	18 (22.2)
Cyclophosphamide	19 (23.4)
Rituximab	26 (32)
IVIG	58 (67.9)
Azathioprine	9 (11.1)
Plasma exchange	2 (2.5)
Other	17 (20.9)
None	5 (6.2)

Early (<3months) combination treatment

NUMBER OF MEDICATIONS USED	N (%)
0	21 (25.9)
1	28 (34.6)
2	18 (22)
>2	5 (6.2)
unknown	9 (11.1)

Rituximab

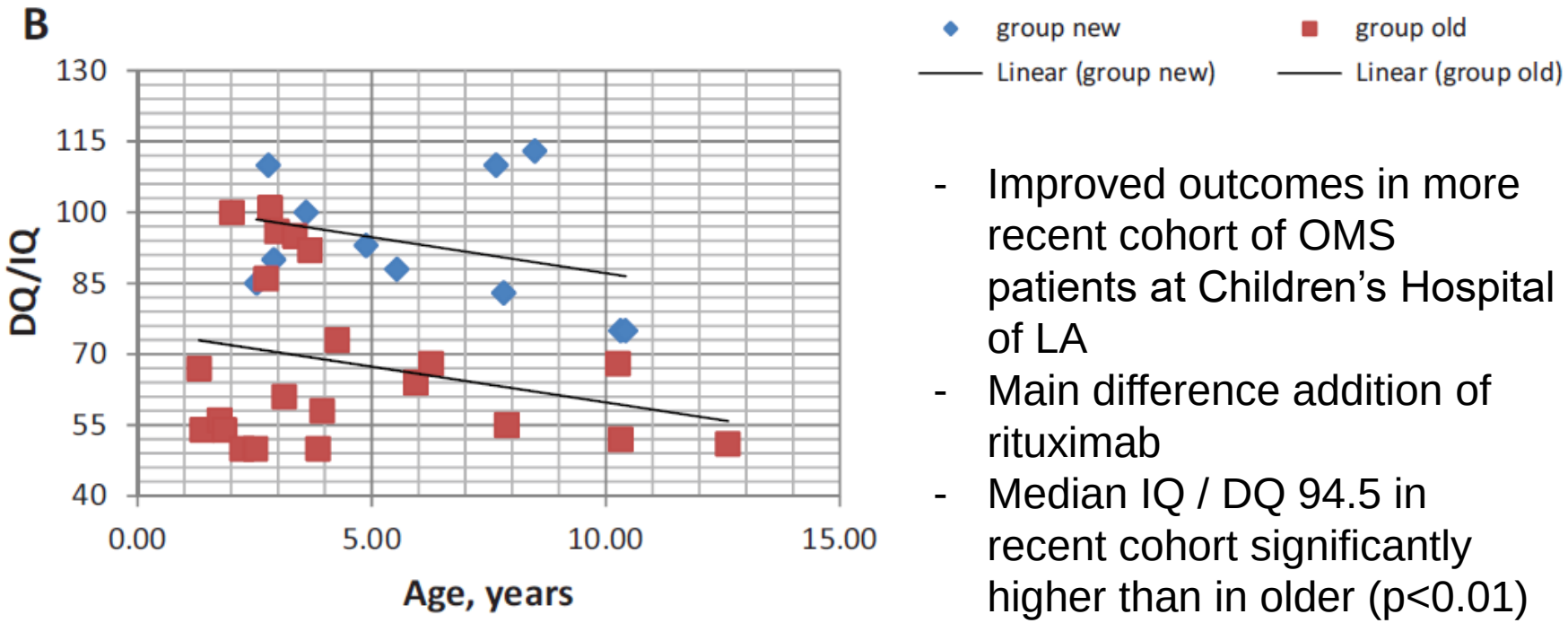
- 26 (32%) received at some point
- Mean time to treatment 5.7 years
- Of those with neuropsychological testing,
  - only 2 received it <12 months from onset and FSIQ was 92 and 98
  - 11 received it >12 months from onset and mean FSIQ was 83 (±16.1) and median FSIQ was 82 (60-105)

Better IQ outcomes in OMS

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.



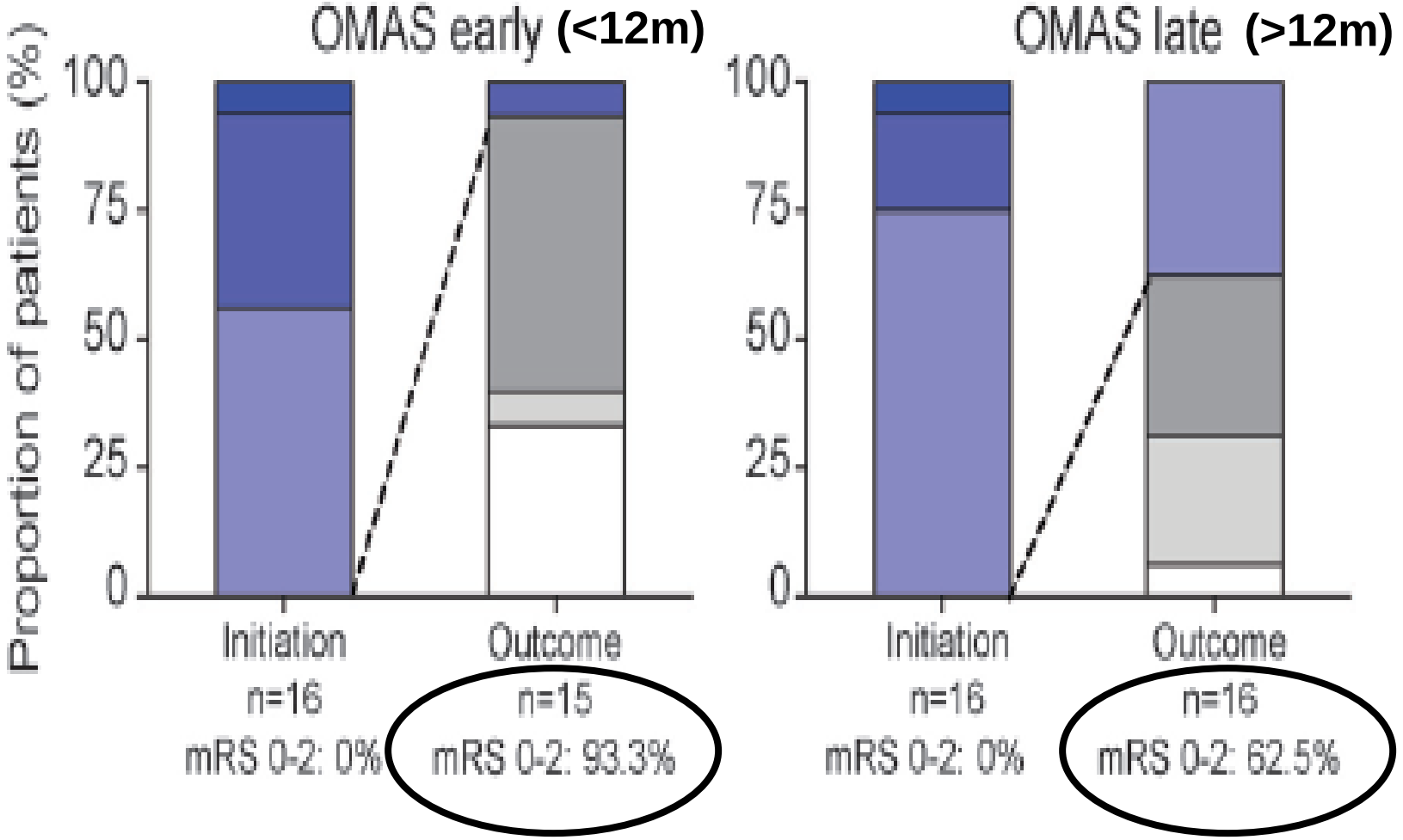
- Improved outcomes in more recent cohort of OMS patients at Children's Hospital of LA
- Main difference addition of rituximab
- Median IQ / DQ 94.5 in recent cohort significantly higher than in older ($p<0.01$)

Mitchell WG, et al. J Child Neurol. 2015;30:976-82

Rituximab in OMS

- Retrospective (looking back) international cohort (group) study of 144 children with pediatric neuro-immunologic disorder treated with rituximab, including 32 patients with OMS
- Divided group into “early” and “late” treatment based on average time from disease onset to treatment initiation
- Trend to better outcome in all conditions including OMS with earlier treatment

Earlier rituximab, better outcome



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

Take home messages for families

- OMS can have a negative impact on long term cognition
- We are unable to predict who is at highest risk for worse cognitive outcomes at the onset of OMS
- Ongoing baseline symptoms and number relapses predict worse outcome
- Earlier rituximab appears to be associated with better outcomes

What to do if concern for relapse?

- Have established local provider who knows patient well and sees regularly (even when doing well!)
- Assess for any signs of infection (ear infection, urinary tract infection, etc)
  - General pediatrician plays key role here!
  - If bacterial infection, treat with antibiotics; sometimes this is sufficient to stop relapse

What to do if concern for relapse?

- Acute treatment options
  - Dexamethasone 20mg/m2/day divided twice a day for 3 days (“pulse”)
  - Other forms of steroids
  - IVIg 1-2g/kg
  - May include moving up scheduled treatments
- Re-assess baseline / chronic treatment
  - If treated with rituximab, have B cells returned?

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