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Long-term neurological outcome in Opsoclonus Myoclonus Ataxia Syndrome- The Indian Experience

Disclosures

- None

Materials and methods:

- Hospital-based, Single center
- Design: Cross-sectional, Observational
- Enrollment: Children diagnosed with Opsoclonus Myoclonus Syndrome and on follow up

Inclusion criteria:

1. Children with confirmed diagnosis of Opsoclonus Myoclonus Ataxia Syndrome.

- *Diagnosis of Opsoclonus Myoclonus Ataxia Syndrome requires the presence of at least 3 of the following:*

(1) opsoclonus;

(2) myoclonus/ataxia;

(3) behavioral change and/or sleep disturbance;

(4) neuroblastoma.

2. Completed immunomodulatory therapy of at least 12 months

Exclusion criteria:

1. If the child had been lost to follow up.
2. If the child has additional neurological insult like encephalitis or significant head trauma either prior or after the diagnosis of OMAS

ANNEXURE 12: UNIT PROTOCOL FOR TREATMENT OF OMS

Opsoclonus Myoclonus Ataxia Syndrome- Protocol ver 2.1

Pediatric Neurology Unit, APC, PGI-Chandigarh, India 160012

***Attach to clinic file*

Clinical diagnosis of OMS: Admit for evaluation and therapy

Step 1: Screen for Neuroblastoma in all cases (irrespective of the presence or absence of any antecedent illness)

1. MRI Chest + Abdomen + Pelvis (Also include neck in infants)
2. PET -CT or DOTATAC PET
3. Brain MRI to rule out an infectious process/tumor presenting as OMS
4. Urine VMA and MIBG if PET not available

Step 2: Assess motor severity using the OMS severity evaluation scale

Step 3: Treatment options

Moderate (up to 12)
ACTH + IVIG (2g/kg-1g/kg/monthly for 6 months and then 6 weekly for 6 months)

Severe (13-18)
ACTH + IVIG + Rituximab 375 mg/m² weekly x 4
CD 2, immunoglobulins and CBC at the end of the fourth dose
Start RTX, 3-4 weeks after surgery
Alternative for very severe cases: Plasmapheresis

Step 4: Assess response: 6 weeks
Adequate response: Improvement by subjective assessment and by the score: 0-1
Inadequate response: persistent signs or symptoms

Inadequate response:
Add agents not tried (IVIG/Dexamethasone/Rituximab/Cyclophosphamide)

Adequate response: Follow up
MRI/PET screen for tumor q 6 mo x 2 yr

Step 5: Relapse:
Dexa 20mg/m² x 3 days oral pulses and consider escalating ongoing therapy if relapses are severe or frequent
Repeat imaging for tumor search

Evaluations

- Full clinical evaluation
- Record of past treatment and relapses
- Neurological assessment
- Cognitive scores (DQ by DP3 or CAT/CLAMS) OR IQ/SQ score by DASII(Bayley SID) or VSMS, MISIC (Wechsler ISC).
- Ataxia evaluation with SARA (Scale for Assessment and Rating for Ataxia) score.
- Child behavior CPMS/ECSA
- **Parental report- 1-2 main concerns with the child**

Table 19. **Primary outcome measures**

Outcome measures	**Measure description**	**Time frame**
Mitchell and Pike OMS severity score	It's an 18-point score to rate the severity of OMS, it will measure residual features of OMS after completing a minimum of 12 months of treatment	12 months or more after treatment initiation with immunomodulators
Proportion of children with normal cognitive outcome	Developmental quotient/ Intellectual quotient/ Social Quotient as applicable using a standard scale – Developmental Profile – 3 scale, Malin's Intelligence Scale for Indian Children, Development assessment scale for Indian Infants, Vineland social maturity scale or equivalent.	12 months or more after treatment initiation with immunomodulators

Table 20. Secondary outcome measures

Outcome measures	**Measure description**	**Time frame**
Mean and median SARA score (Scale for Assessment and Rating for Ataxia)	It is a score that quantitates ataxia	12 months or more after treatment initiation with immunomodulators
The proportion of children with behavioral problems and the type of behavioral problems	Childhood Psychopathology Measurement Scale (CPMS) or, Early Childhood Screening Assessment Score or any other score as per the age of the child	12 months or more after treatment initiation with immunomodulators
The proportion of children with language problems as assessed on the CLAM scale (Clinical Linguistic and Auditory Milestone Scale)	CLAM scale (Clinical Linguistic and Auditory Milestone Scale) is a measure of the Capute scale and is used to quantitate language development up to 36 months of age	12 months or more after treatment initiation with immunomodulators

Objectives:

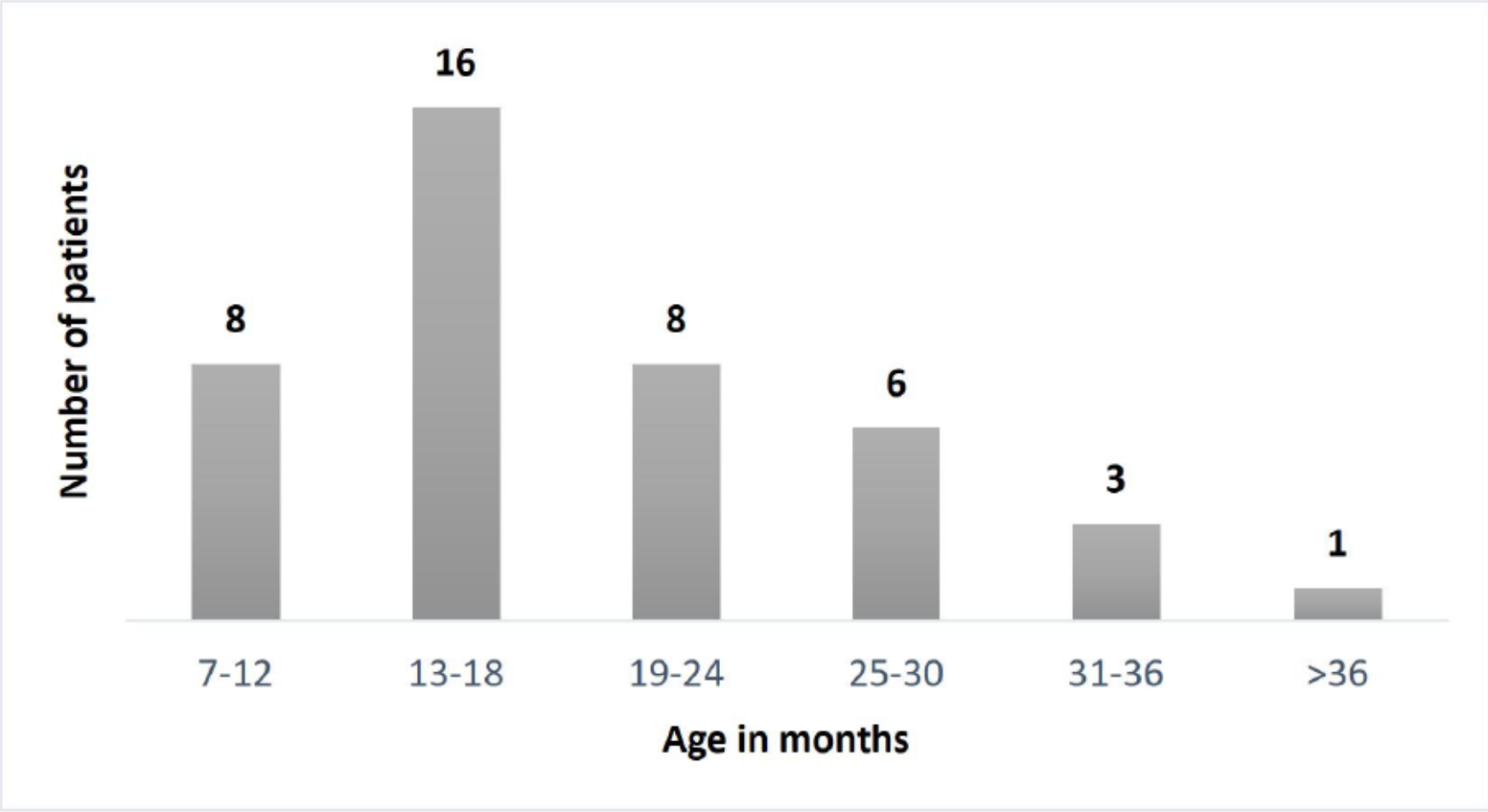
Primary objective:

- To determine proportion of children with good cognitive outcome after completing treatment for OMAS.

Secondary objectives:

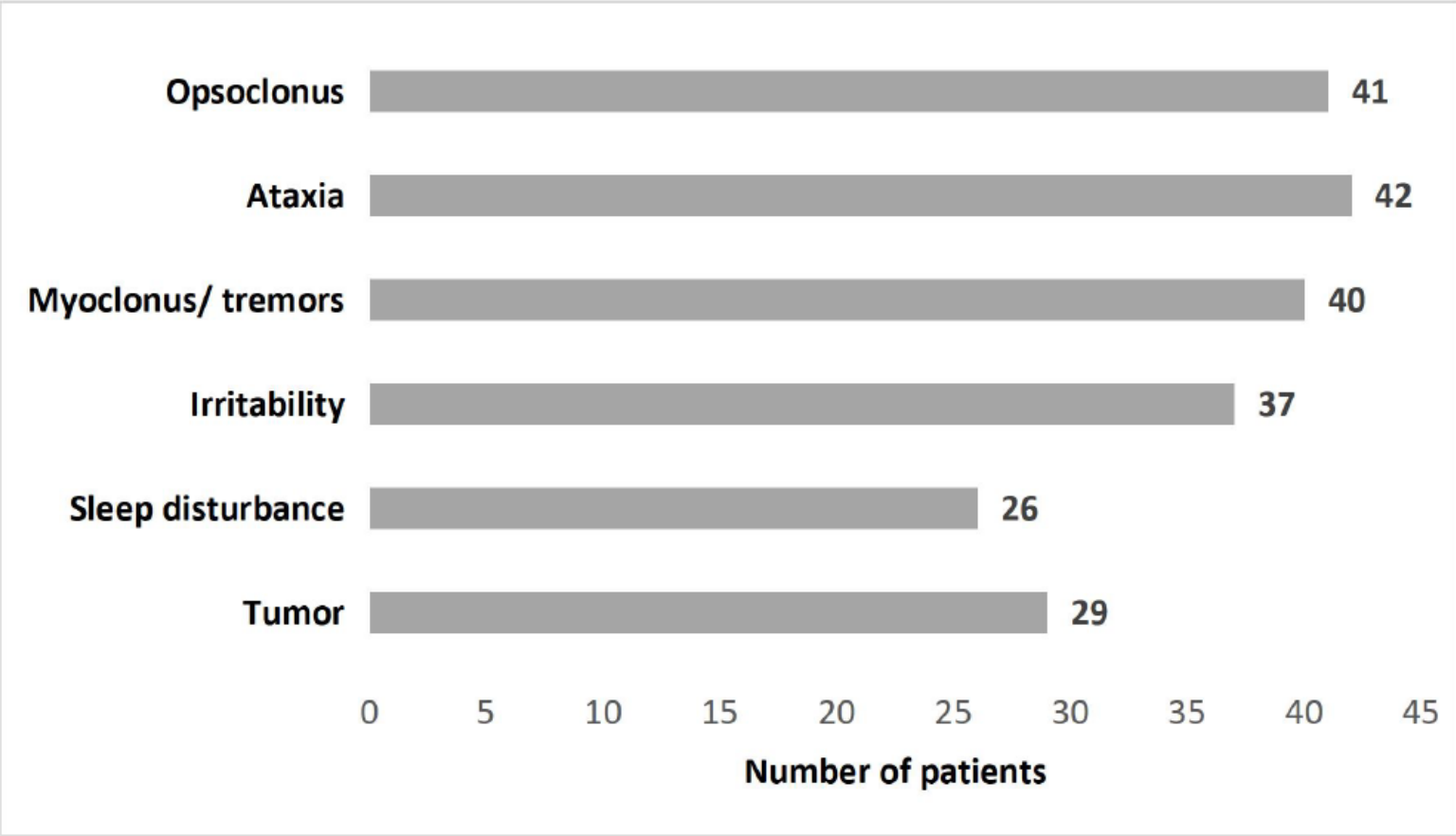
- To determine the mean SARA (Scale for Assessment and Rating for Ataxia) score in children.
- To determine predictors of poor cognitive outcome in children.

42 children (Age at Onset)



- M: F: 45: 55
- Median age:
- Mean: 19 ± 8.5
- Median: **18** (14 – 24)
- Range: 7 – 49

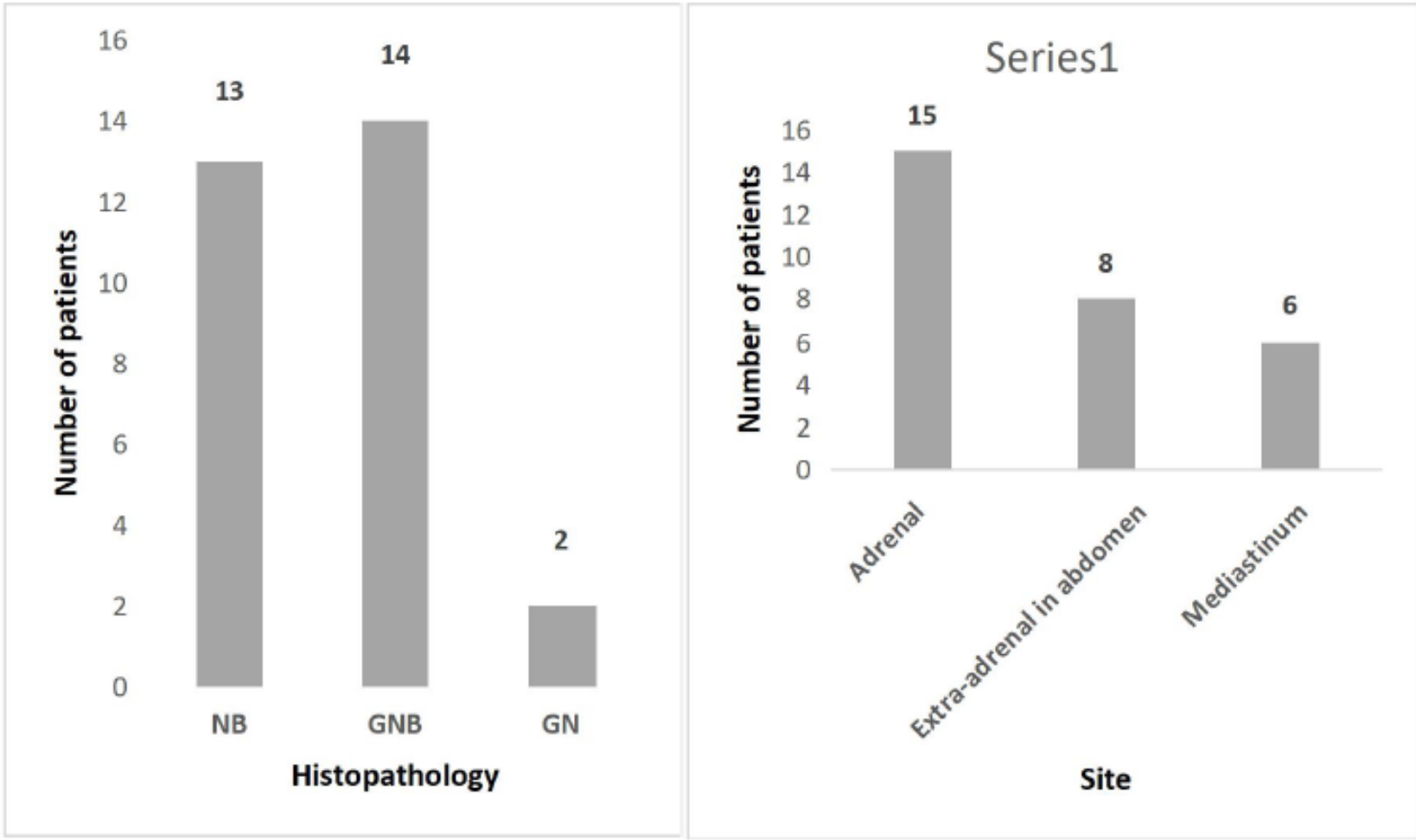
Clinical features



- Tumor*, N (%) 29 (69%)
- Auto-immune disease in first-degree relatives, N (%) 6 (14%)
- Affected relative: Mother 6 (100%)

Krug et al-64%, Mitchell et el-60%

Figure 8. Tumor histopathology and site in 29 tumor-associated OMS



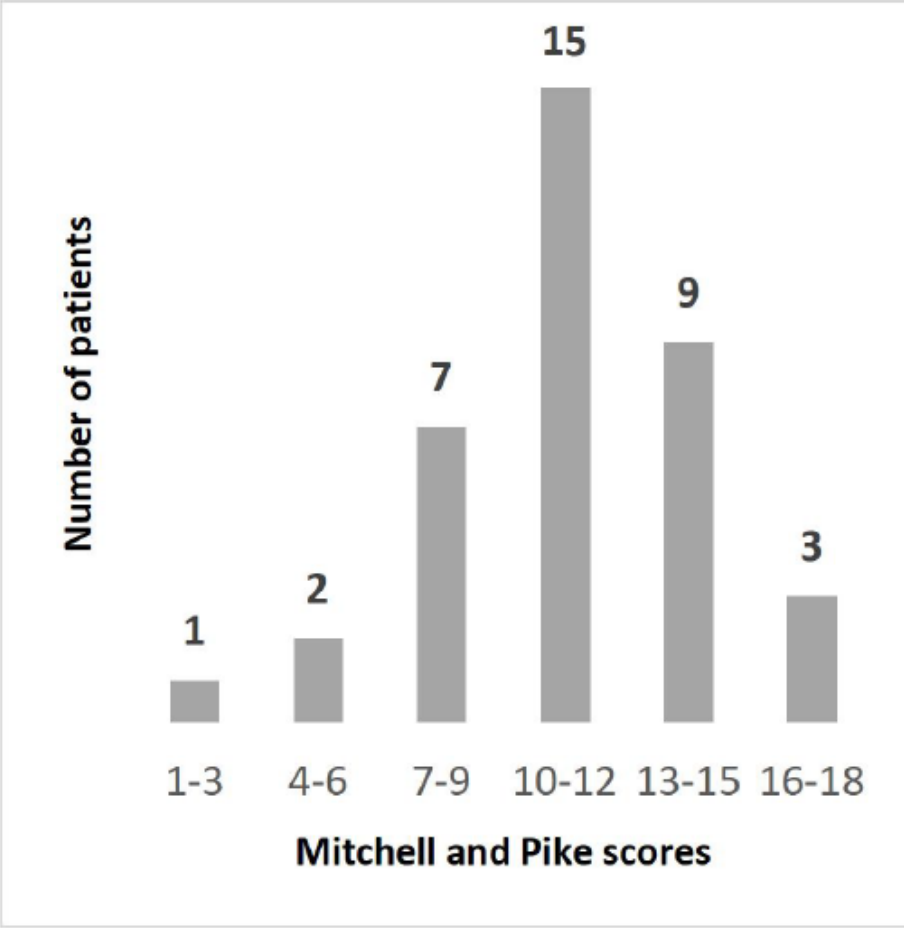
NB – Neuroblastoma, GNB – Ganglioneuroblastoma, GN – Ganglioneuroma, SR – Supra-renal region

Tumor detection rates, N (%)	
PET, N=29	29 (100%)
CT, N=8	8 (100%)
MRI, N=19*	16 (84%)
USG, N=19#	5 (26%)
MYC-N amplification, N (%)	
Yes	2 (7%)
No	27 (93%)
Treatment, N (%)	
Tumor resection	29 (100%)
Chemotherapy	2 (7%)

**3 were PET-positive, and MRI-negative*

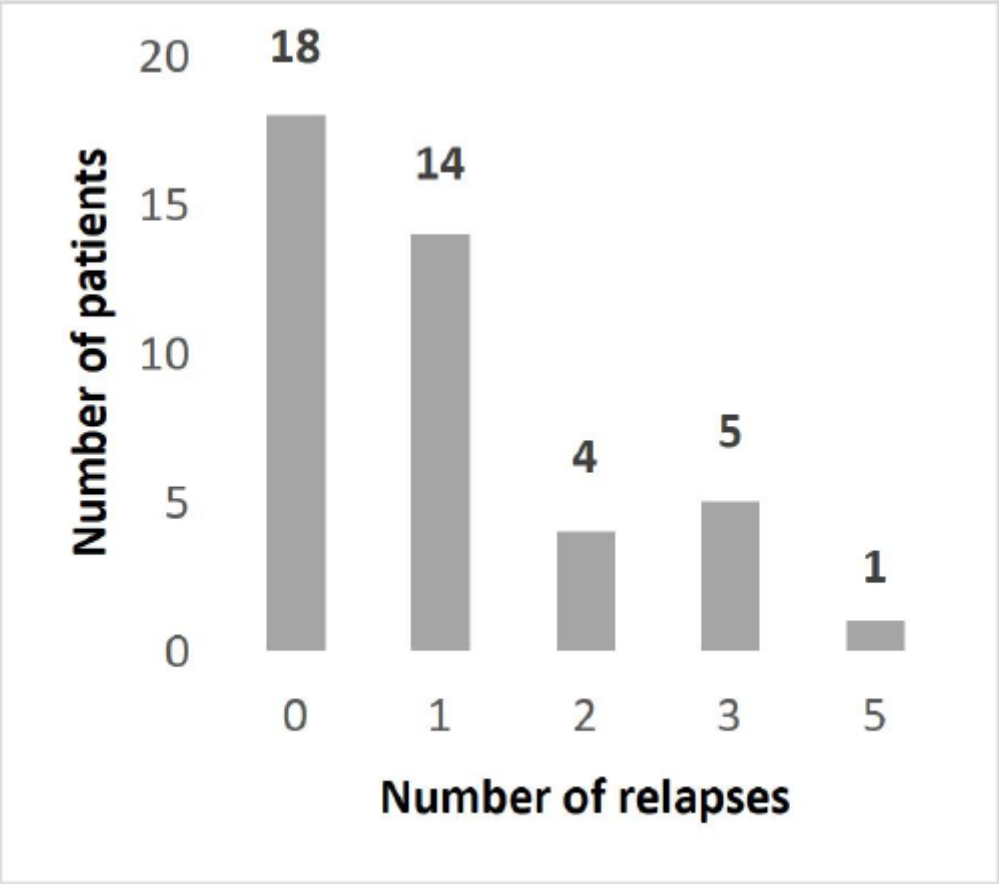
#14 were PET-positive, and USG-negative

Figure 5. Mitchell and Pike scores of 37



- Median score -12(9-13)
- Mild OMS (1-6): 3(8%)
- Moderate OMS (7-12): 22 (59.5%)
- Severe OMS (13-18)- 12(32.5%)

Relapses



Relapse rate: 57%

Follow-up from disease onset –
Median (42.5 months)
Range: 14 to 89 months.

Table 25. Comparison between the characteristics of monophasic and relapsing OMS

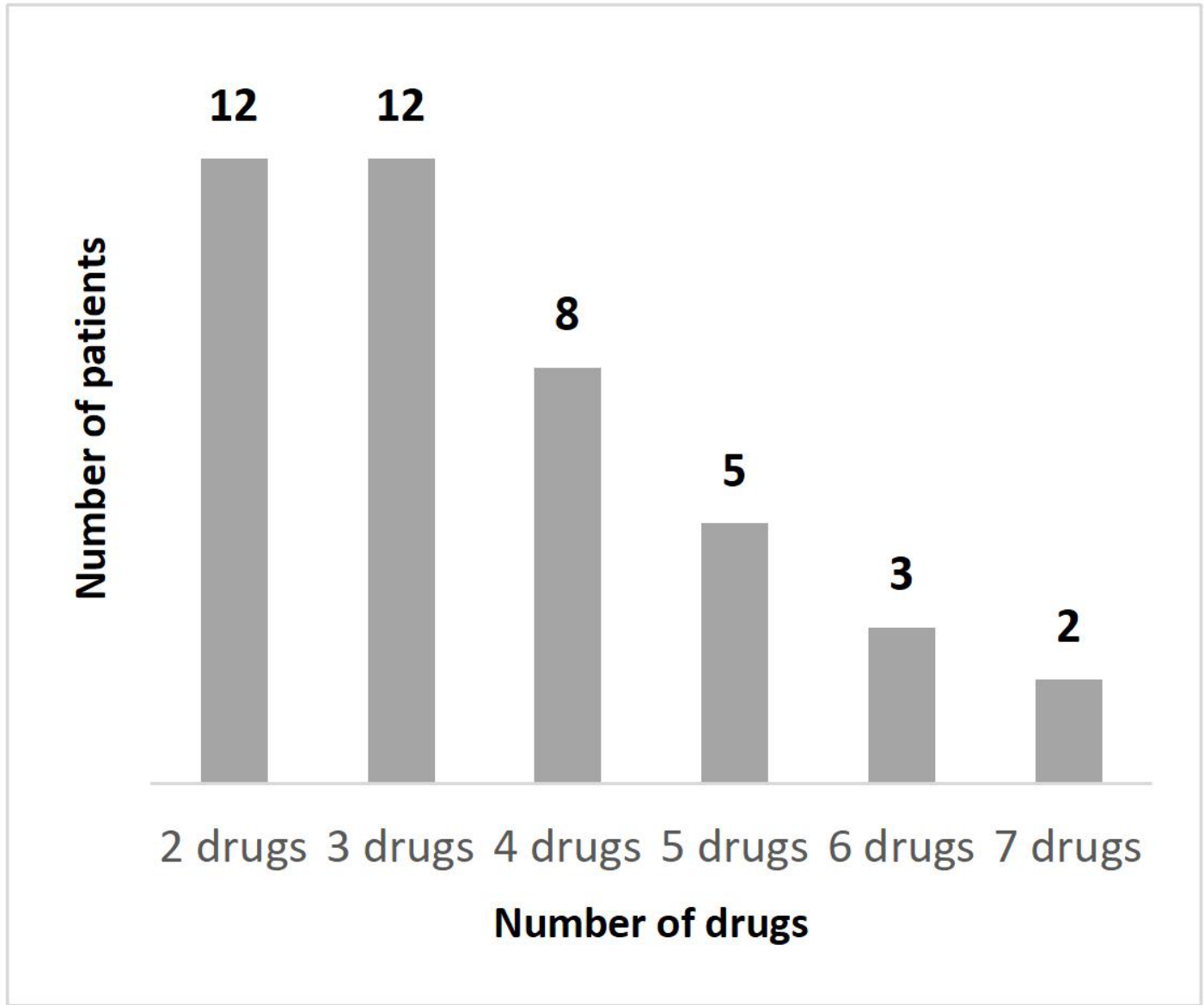
	Monophasic OMS, N=17	**Relapsing OMS, N=25**	**p-value**
Age at onset, months*			
Mean ± SD	20.6 ± 11.1	17.2 ± 5.7	0.390
Median (IQR)	21 (13 – 27)	17 (14 – 20)	
Female, N (%)	11 (64.7%)	12 (48%)	0.353
Tumor present, N (%)	8 (47%)	21 (84%)	0.018
Treatment lag, weeks*			
Mean ± SD	14.8 ± 14.2	4.9 ± 4.5	0.173
Median (IQR)	5 (2 – 25)	3 (3 – 4)	
OMS peak score at onset			
Mean ± SD	9.3 ± 3.5	12.7 ± 2.5	0.002
Median (IQR)	9 (7 – 12)	12 (11 – 14)	
Total Treatment duration, months*			
Mean ± SD	15.4 ± 2.7	26.3 ± 8	0.001

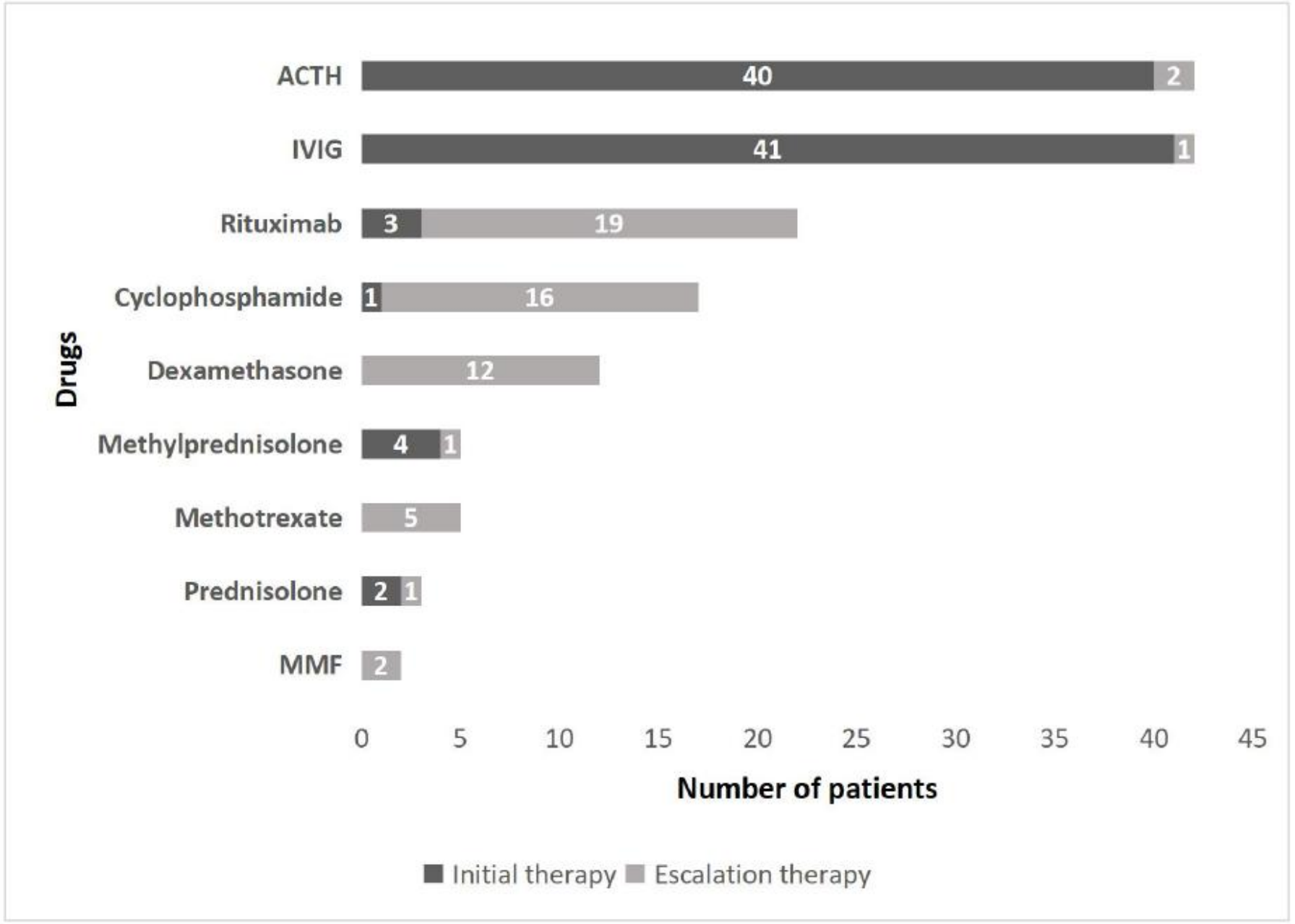
months*			
Mean ± SD	15.4 ± 2.7	26.3 ± 8	0.001
Median (IQR)	15 (13 – 16)	27 (20 – 32)	
Steroid therapy duration, months*			
Mean ± SD	15.4 ± 2.7	24.9 ± 8.1	<0.001
Median (IQR)	15 (13-16)	25 (18 – 32)	
IVIG therapy duration, months*			
Mean ± SD	14.8 ± 4.3	18.9 ± 9.6	0.031
Median (IQR)	14 (13 – 16)	20 (14 – 26)	
Number of drugs used*			
Mean ± SD	2.7 ± 0.8	4 ± 1.5	0.001
Median (IQR)	3 (2 – 3)	4 (3 – 5)	
OMS score at follow-up*			
Mean ± SD	0.6 ± 0.6	1.3 ± 0.9	0.005
Median (IQR)	1 (0 – 1)	1 (1 – 2)	

**Data non-parametrically distributed. p-value was derived from the Mann-Whitney U test.*

Table 27. Comparison between characteristics of OMS with tumor and without tumor

	Tumor, N=29	**No tumor, N=13**	**p-value**
Age at onset, months			
Mean ± SD	18.1 ± 7.5	21.8 ± 10.1	0.268
Median (IQR)	17 (14 – 21.5)	22 (14 – 25.5)	
Female, N (%)	16 (55.2%)	7 (53.8%)	1.000
Relapses, N (%)			
Relapsing course	21 (72%)	4 (31%)	0.018
Median (IQR)	1 (0 – 2)	0 (0 – 1)	
Treatment lag, weeks			
Mean ± SD	6.4 ± 8.6	12.7 ± 13.1	0.129
Median (IQR)	3 (2 – 4)	4 (3 – 26)	
OMS peak score at onset*			
Mean ± SD	12.2 ± 3.1	8.6 ± 2.7	0.03
Median (IQR)	12 (11 – 14)	7.5 (6.75 – 12)	
Treatment duration, months			
Mean ± SD	23.4 ± 8.2	18.5 ± 7.9	0.064
Median (IQR)	21 (16 – 30.5)	16 (13 – 21)	
Steroid therapy duration, months			


12
12
8
5
3
2
Number of patients
2 drugs
3 drugs
4 drugs
5 drugs
6 drugs
7 drugs
Number of drugs


ACTH
IVIG
Rituximab
Cyclophosphamide
Dexamethasone
Methylprednisolone
Methotrexate
Prednisolone
MMF
Drugs
40
2
41
1
3
19
1
16
12
4
1
5
2
1
2
0
5
10
15
20
25
30
35
40
45
Number of patients
Initial therapy
Escalation therapy

	ACTH + IVIG
	ACTH only
	IVIG only
	ACTH + Dexamethasone
	IVIG + Dexamethasone
	IVIG + Prednisolone
	Methotrexate + Dexamethasone
	ACTH + Methotrexate + Dexamethasone
	Prednisolone only
	ACTH + Mycophenolate mofetil
	ACTH + IVIG + Dexamethasone
	ACTH + IVIG + Dexamethasone + Methotrexate
	Dexamethasone + Mycophenolate mofetil
	Ongoing treatment
↓	Relapse
<	Only one dose of IVIG
©	Cyclophosphamide
*	Rituximab
^	Methylprednisolone pulse
End	End of treatment
Interruption	Treatment interruption
Phenotype	1 – Monophasic, 2 – Intermittent, 3 - Chronic

S	P										
08	1										
13	1	<©©©	©©©	©							
22	1		©	© © ©	©						
28	1	****									
		↓									
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02	1										
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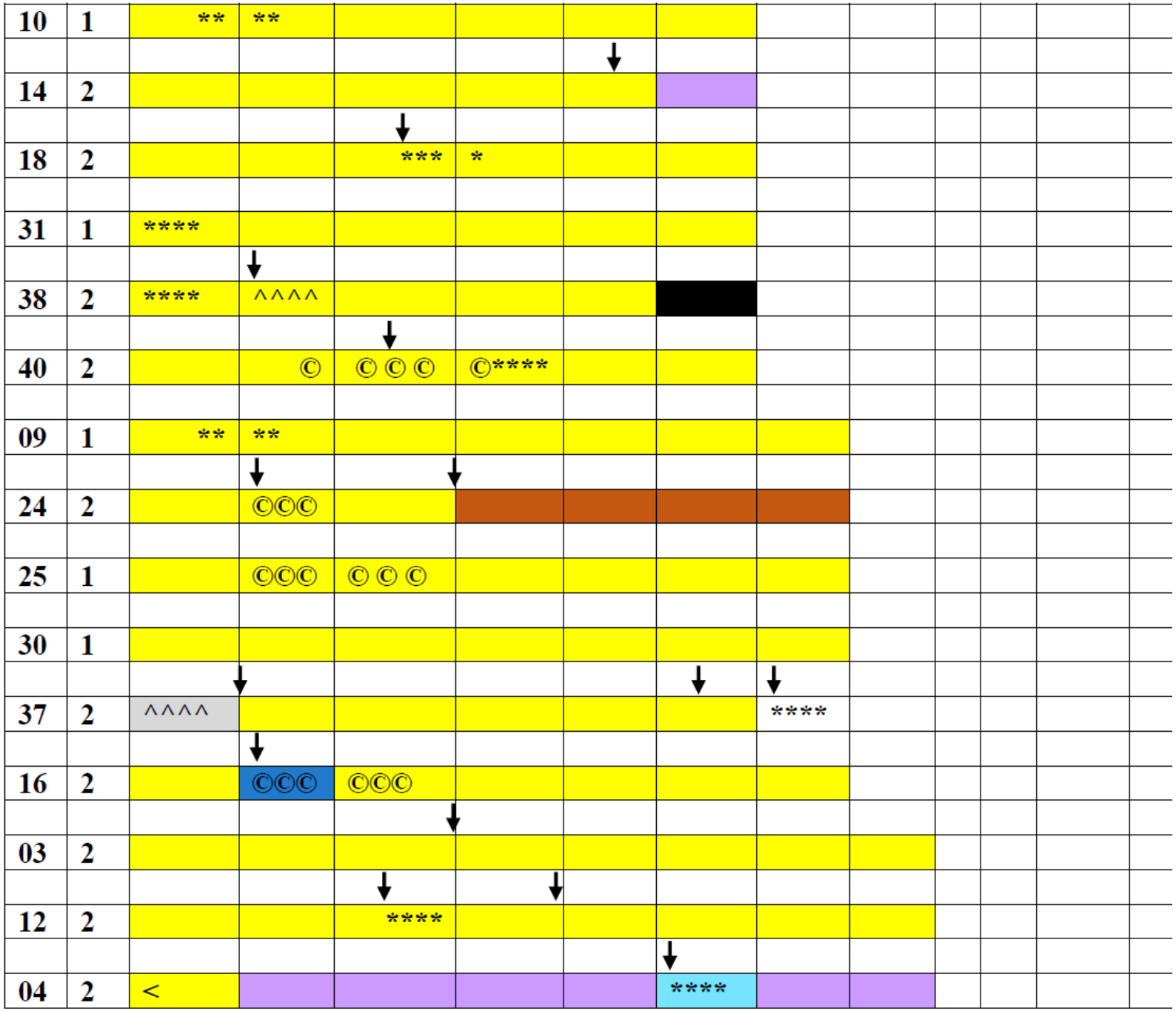
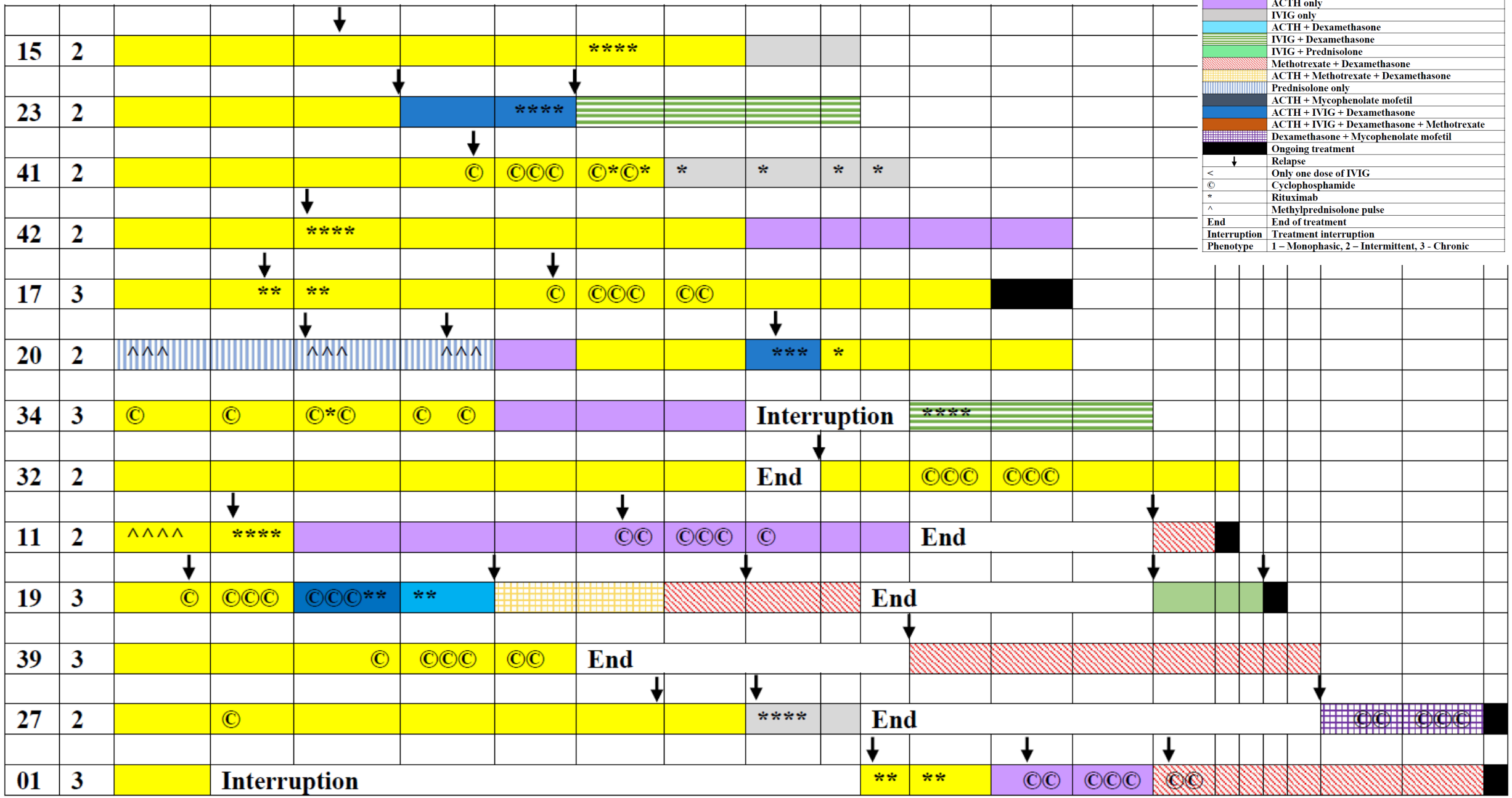
06	1										
07	1	****	©	© © ©	© © ©						
21	1										
26	1	^^^			©©©	©©©					
36	1										

	ACTH + IVIG
	ACTH only
	IVIG only
	ACTH + Dexamethasone
	IVIG + Dexamethasone
	IVIG + Prednisolone
	Methotrexate + Dexamethasone
	ACTH + Methotrexate + Dexamethasone
	Prednisolone only
	ACTH + Mycophenolate mofetil
	ACTH + IVIG + Dexamethasone
	ACTH + IVIG + Dexamethasone + Methotrexate
	Dexamethasone + Mycophenolate mofetil
	Ongoing treatment
↓	Relapse
<	Only one dose of IVIG
©	Cyclophosphamide
*	Rituximab
^	Methylprednisolone pulse
End	End of treatment
Interruption	Treatment interruption
Phenotype	1 – Monophasic, 2 – Intermittent, 3 - Chronic



	ACTH + IVIG
	ACTH only
	IVIG only
	ACTH + Dexamethasone
	IVIG + Dexamethasone
	IVIG + Prednisolone
	Methotrexate + Dexamethasone
	ACTH + Methotrexate + Dexamethasone
	Prednisolone only
	ACTH + Mycophenolate mofetil
	ACTH + IVIG + Dexamethasone
	ACTH + IVIG + Dexamethasone + Methotrexate
	Dexamethasone + Mycophenolate mofetil
	Ongoing treatment
↓	Relapse
<	Only one dose of IVIG
©	Cyclophosphamide
*	Rituximab
^	Methylprednisolone pulse
End	End of treatment
Interruption	Treatment interruption
Phenotype	1 – Monophasic, 2 – Intermittent, 3 - Chronic


15 2
23 2
41 2
42 2
17 3
20 2
34 3
32 2
11 2
19 3
39 3
27 2
01 3
Interruption
End
ACTH + IVIG
ACTH only
IVIG only
ACTH + Dexamethasone
IVIG + Dexamethasone
IVIG + Prednisolone
Methotrexate + Dexamethasone
ACTH + Methotrexate + Dexamethasone
Prednisolone only
ACTH + Mycophenolate mofetil
ACTH + IVIG + Dexamethasone
ACTH + IVIG + Dexamethasone + Methotrexate
Dexamethasone + Mycophenolate mofetil
Ongoing treatment
Relapse
< Only one dose of IVIG
© Cyclophosphamide
* Rituximab
^ Methylprednisolone pulse
End End of treatment
Interruption Treatment interruption
Phenotype 1 – Monophasic, 2 – Intermittent, 3 - Chronic

Treatment lag (weeks)

- Monophasic: 5(2-25)
- Relapsing- 3(3-4)
- Tumor: 6
- No tumor- 12

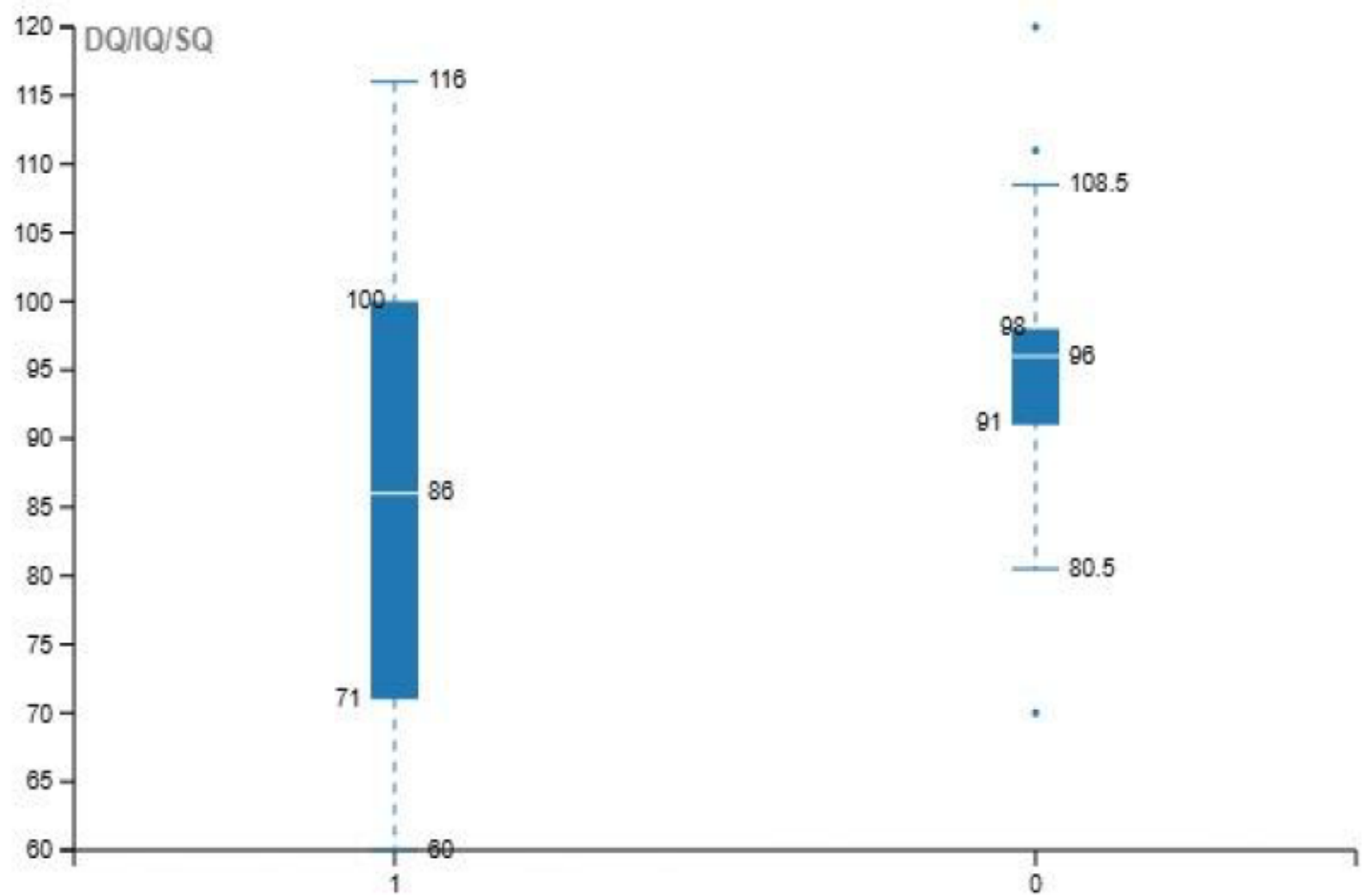
- 85- 60%
- < 85- 40%

Total number of patients	**42**	
IQ scales used, N (%)		
VSMS(SQ)	38 (90.5%)	
MISIC(IQ)	3 (7.2%)	
DP3(DQ)	1 (2.4%)	
IQ scores, N (%)	**Frequency**	**Mean age at OMS onset, months**
55-69 (Mild mental retardation)	6 (14.3%)	16 ± 6.8
70-84 (Borderline IQ)	11 (26.2%)	16.1 ± 6.1
85-99 (Below average IQ)	14 (33.3%)	23.2 ± 10.5
≥100 (IQ average and above)	11 (26.2%)	19.3 ± 7.2
Mean ± SD, overall	88.6 ± 15.6	
Median (IQR), overall	89 (76 – 100.8)	
Range, overall	60 – 120	

- Brunklaus et al- 76(25)
- De Grandis- 78(14)

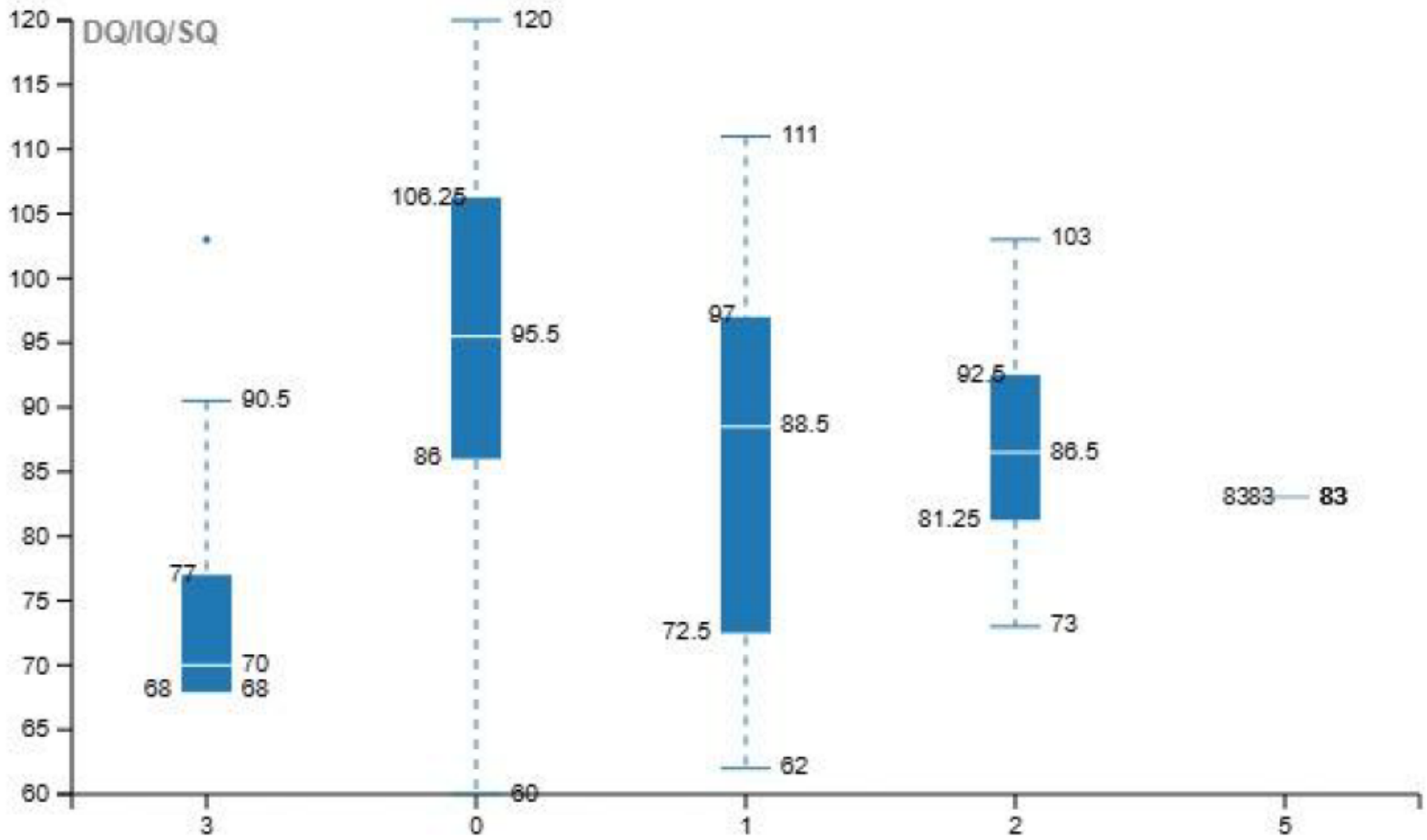
≥100 (IQ average and above)	11 (26.2%)	19.3 ± 7.2
Mean ± SD, overall	88.6 ± 15.6	
Median (IQR), overall	89 (76 – 100.8)	
Range, overall	60 – 120	
Mean ± SD, monophasic OMS	97.4 ± 13.2	
Median (IQR), monophasic OMS	96 (86 – 107.5)	
Mean ± SD, relapsing OMS	82.3 ± 15.1	
Median (IQR), relapsing OMS	83 (69 – 97)	
p-value	0.004	
Mean ± SD, OMS with tumor	85.9 ± 16.2	
Mean ± SD, OMS without tumor	94.9 ± 12.7	
p-value	0.060	

Figure 14. The distribution of IQ scores in tumor and no-tumor groups



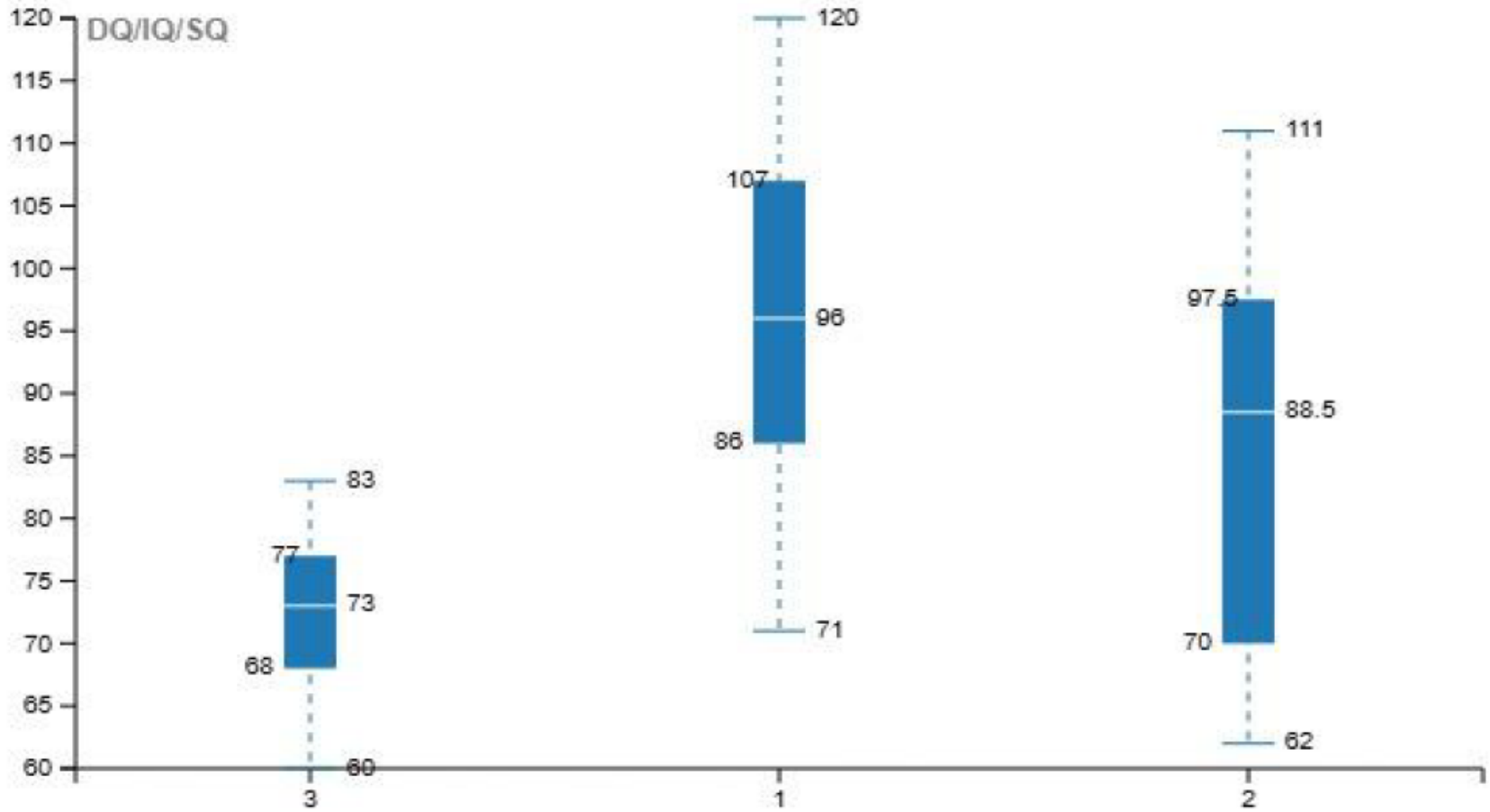
x-axis: 1 – Tumor present, 0 – No tumor. y-axis: IQ scores/equivalent

Figure 15. The distribution of IQ scores based on the number of relapses



x-axis: Number of relapses. y-axis: IQ scores/equivalent

Figure 16. The distribution of IQ scores based on the clinical phenotype



x-axis: 1 – monophasic course, 2 – intermittent course, 3 – chronic course. y-axis: IQ scores/equivalent

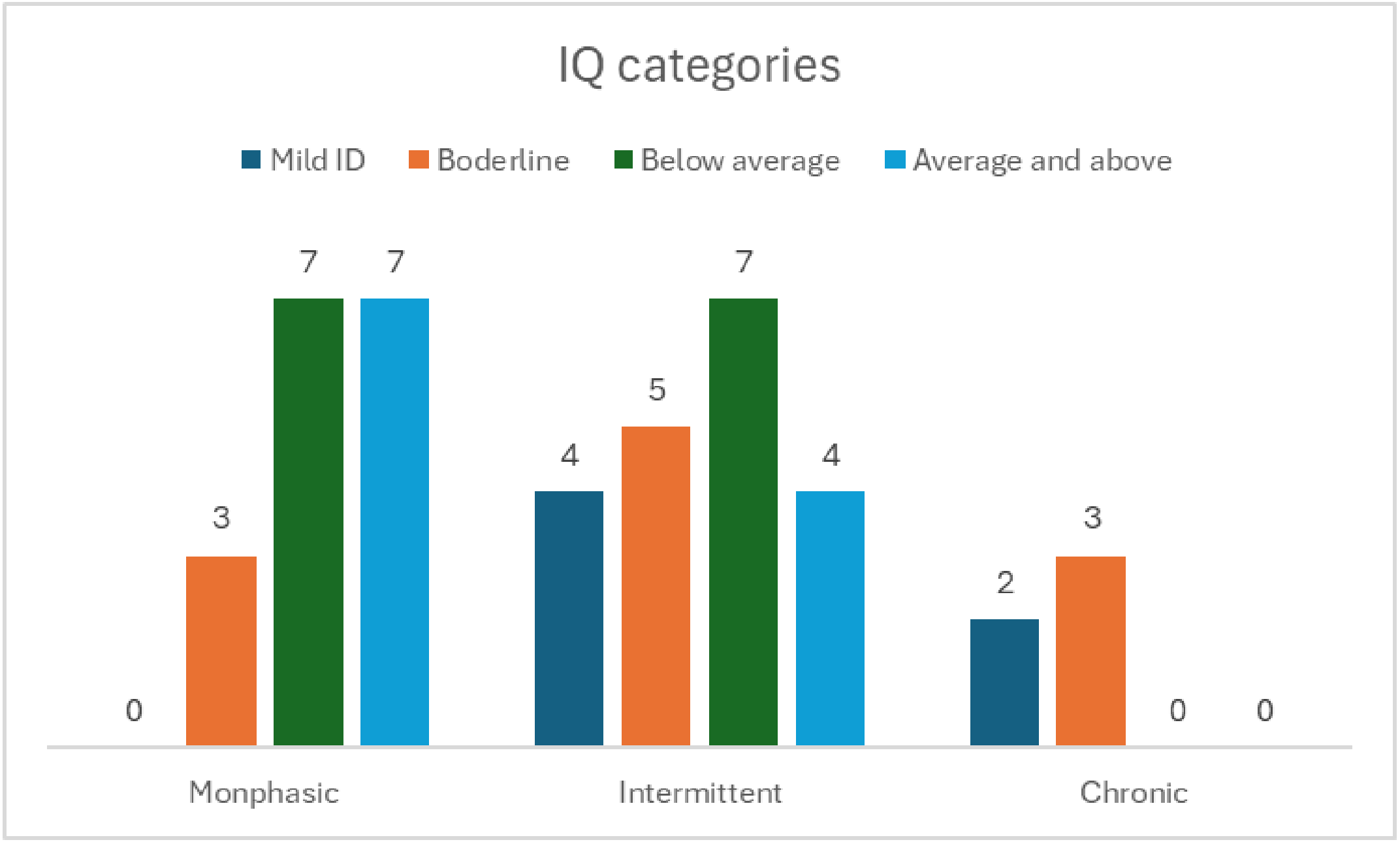

IQ categories
Mild ID
Boderline
Below average
Average and above
0
3
7
7
4
5
7
4
2
3
0
0
Monphasic
Intermittent
Chronic

Table 35. Predictors of poor IQ scores in 42 patients with OMS

	IQ < 85, N=17	IQ ≥85, N=25	p-value
Age at onset, months			
Mean ± SD	16.1 ± 6.1	21.5 ± 9.2	0.041
Median (IQR)	16 (11.5 – 20)	19 (15 – 26)	
Female, N (%)	9 (53%)	14 (56%)	1.000
Tumor present, N (%)	14 (82%)	15 (60%)	0.179
Relapses, N (%)			
Monophasic course	4 (24%)	14 (56%)	0.012
Relapsing course	13 (76%)	11 (44%)	
Median (IQR)	1 (0.5 – 3)	0 (0 – 1)	
Treatment lag, weeks			
Mean ± SD	7.7 ± 10.7	8.8 ± 10.6	0.444
Median (IQR)	3 (2 – 8)	4 (2 – 12)	
OMS peak score at onset			
Mean ± SD	12.6 ± 2.8	10.3 ± 3.5	0.038
Median (IQR)	13 (12 – 14)	10.5 (7.75 – 12)	

Mean ± SD	12.6 ± 2.8	10.3 ± 3.5	0.038
Median (IQR)	13 (12 – 14)	10.5 (7.75 – 12)	
Total treatment duration, months			
Mean ± SD	26.9 ± 9.2	18.5 ± 5.8	0.008
Median (IQR)	30 (17 – 33)	17 (14 – 20.5)	
Steroid therapy duration, months			
Mean ± SD	25.4 ± 9.5	18.3 ± 5.7	0.024
Median (IQR)	26 (15.5 – 33)	17 (14 – 20)	
IVIG therapy duration, months			
Mean ± SD	19.1 ± 10.6	16.3 ± 5.5	0.520
Median (IQR)	20 (10.5 – 27.5)	16 (13 – 20)	
Number of drugs used			
Mean ± SD	4.4 ± 1.5	3 ± 1	0.002
Median (IQR)	4 (3 – 6)	3 (2 – 4)	
OMS score at follow-up			
Mean ± SD	1.6 ± 0.8	0.6 ± 0.6	<0.001
Median	2 (1 – 2)	1 (0 – 1)	

Table 36. Results showing multivariate linear regression of predicting the cognitive outcome of 42 patients with OMS

Predictors	**p-value**	**Odd's ratio**	**95% confidence interval**
Age at onset	0.531	1.05	0.90 – 1.23
Gender	0.954	0.95	0.16 – 5.72
Treatment lag	0.618	0.97	0.88 – 1.08
Number of drugs	0.079	0.47	0.20 – 1.09
Total treatment duration	0.776	0.98	0.84 – 1.14
Tumor presence	0.327	2.84	0.35 – 22.90
Relapsing OMS	0.917	1.15	0.08 – 15.98
OMS score at follow-up	0.076	0.26	0.06 – 1.15

Table 38. Problems reported by parents in 42 children with OMS

Total number of patients	42
Number of problems reported, N (%)	
Zero problem	10 (24%)
One problem	26 (62%)
Two problems	6 (14%)
Problems reported by parents*, N (%)	
Nil	10 (24%)
Misarticulation/	24 (57.1%)
Language delay	6 (14.3%)
Behavioral issues	7 (16.8%)
Learning problems in school	2 (4.8%)

**Percentages do not tally to 100 because the problems are not mutually exclusive*

- Tate et al: n=105, 50-75%
- Brunklaus et al: 101- 66%
- Klien et al: n=10- 50% slurring

audio

Table 42. Results of screening tests for behavior in 42 children with OMS

Total number of patients	**42**
Number of patients with significant scores, N (%)	**11 (26%)**
CPMS scale (score more than 9)	8 (19%)
ECSA scale (score more than 8)	3 (7%)
CPMS scores, N (%)	
Not applicable	14 (33.3%)
0-9	19 (45.2%)
10-20	8 (19%)
21-30	1 (2.4%)
Median CPMS score	3 (1 – 8.2)
CPMS domains with significant scores, N (%)	**11**
Low intelligence, behavior problems	7 (87.5%)
Conduct disorder	7 (87.5%)
Special symptoms	4 (50%)
Anxiety	2 (25%)
Psychotic symptoms	1 (12.5%)
Physical illness	1 (12.5%)
Depression	1 (12.5%)
Somatization	1 (12.5%)
ECSA scores (%)	
Not applicable	19 (45%)
0-8	18 (42.8%)
9-20	5 (11.9%)

STRENGTHS

 Prospective, Structured assessments in patients with OMS.

 Provides cognitive outcomes in a predominantly escalating protocol.

LIMITATIONS

- There were eligible children we could not enroll
- Articulation problems - better assessed with specific tools
- SQ is a surrogate marker of Intellectual Quotient. A better outcome scale - a Full-scale IQ (FSIQ), which includes performance and verbal scales.

Conclusions

- In children with OMS, most of whom were treated with an escalating protocol of immunomodulation
- **Median IQ: 89**
- Better than those reported in historical cohorts treated with less intensive regimens
- However, 40% <85 , Only 26% average or above average IQ
- **Speech and articulation problems**.

- The residual deficits:
  - Tumors
  - Relapses
  - Initial severity of OMS
  - Younger age

Thank you

Pediatric Neurology	Manoj K Abhishek Pandey Senior Residents
	Jitendra Sahu, Renu Suthar, Arushi Saini
Pediatric Surgery	Nitin Peters
Psychologists	Rajni Sharma,
	Gagandeep Singh,
Nuclear Medicine	Rajender Kumar
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