Juvenile Myasthenia gravis:
clinical course and outcome in patients from a single neuromuscular centre in Germany

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Juvenile Myasthenia Gravis (JMG)

- antibodies (Ab) against postsynapric membrane proteins:
  - Acetylcholine receptor (AChR), muscle-specific tyrosine- kinase (MuSK), low receptor protein (LRP4) → impaired neuromuscular transmission
- clinical presentation:
  - ocular symptoms: ptosis, ophthalmoplegia, double vision
  - generalized symptoms: bulbar symptoms, facial hypomimia, generalized muscle weakness, respiratory involvement possible

  → myasthenic crises

Juvenile Myasthenia Gravis - Therapy

- therapy – derived from adults
  - acetylcholinesterase inhibitors/immunosuppressive agents/plasmapheresis/intravenous immunoglobulin (IvIG)/new agents (biologica)?
  - AChR-Ab positive myasthenia – thymectomy important treatment option in adults (Wolfe GI, N Engl J Med. 2016)
  - due to active role of the thymus gland in immune system developement – consideration in performing thymectomy in prepubertal children
- data concerning optimal therapeutic strategies in JMG are still spared

Juvenile Myasthenia Gravis - Therapy

- in case of persistent clinical symptoms after intensive drug therapy or severe muscular weaknees - no clear therapeutic pathway exist
- to date: 8 patients have been described who received Rituximab therapy for severe JMG, 6/8 improved:
  - Koul et al. , Pediatr Neurol. 2012: f, 4 years, seronegative
  - Maddison et al., J Neurol Neurosurg Psychiatry 2011 : 4xf (2-14 years), 3xAChR Ab, 1x MuSK Ab positive
  - Linderberg etl al., Acta Neurol Scand 2010: f, 12 years, AChR Ab positive
  - Tzaribachev N et al., Cases J. 2009 : f, 13 years, AChR Ab positive
  - Wylam et al., J Pediatr 2003 : f, 9 years AChR Ab pos.

Methods

- retrospective analysis of patients with JMG in our neuromuscular centre from 01/2009-12/2014
- age at symptom onset, time of diagnosis, specific antibodies, applied therapy, duration of immunosuppressive therapy
- assessment of **severity of disease** according to modified Osserman classification prior and post thymectomy: grade I – IV (Tracy et al, 2009, Heng et al, 2014)
- assessment of **time** and **response to thymectomy** via myasthenia scale of Millichap and Dodge: A – E (Millichap et al., 1960)

Results I: patients

- 21 patients: 19 female, 2 male
  - onset:
    - 18 months - 15 years
    - 13 prepubertal
    - ocular symptoms: 7, 4 of them progressed to generalised MG
    - generalised symptoms: 14
  - specific antibodies (tested in all):
    - AChR: 18, MuSK:1
    - 2 patients with isolated ocular symptoms: negative

Results II: therapy

- pyridostigmine: 21/21
- steroids: 19/21
- azathioprine: 12/21
- mycophenolate mofetil: 2/21
- cyclosporine A: 2/21
- IvIG: 12/21
- plasmapheresis: 4/21
- thymectomy: 17/21 (median age 10 years, 3months, range 4 – 15 years)

Results III: disease severity prior/post thymectomy

Nr./Sex	Age at onset	Age at diagnosis	Clinical symptoms (Ossermann) prior to Tx	Medication prior to Tx	Age at Tx	Clinical symptoms post Tx (Ossermann)	Clinical response to Tx (Millichap)	Medication 6 months after Tx
1/f	1 y 6m	1y 6m	IIb	PS, ST	6 y	I a	B	PS, AZA
2/m	2 y	2 y m	IIa	PS, ST	6 y 3 m	I a	B	PS, ST
3/f	1a 8m	2y 1m	IIb	PS,ST,AZA	4y 3 m	Ia	B	PS, AZA
4/f	8y	12a 11m	IV	PS, ST, AZA, PP	13y 8 m	IIb	C	PS, AZA
5/f	9a 2m	9 y m	IIa	PS, ST, AZA	10 y 11 m	0	A	PS
6/f	11a 7m	12y	III	PS, ST	12y	IIa	B	NN
7/f	10y 1m	10 y 1m	Ib	PS, ST, AZA	12 y	Ia	A	PS, AZA
8/f	8y 1m	8y 2m	IV	PS, ST, PP, IvIG, MMF	10 y, 2 m	Ib	B	PS. MMF
9/f	12y	13y	IIb	PS, ST	14 y 8 m	O	A	PS
10/f	11y	12y	IIa	PS, ST	12 y 11 m	O	A	PS
11/f	13 y 8m	15y	IIb	PS, ST, AZA	15 y 3 m	O	B	PS
12/m	6y	7y 10m	IV	PS, ST, AZA, PP	8 y 6 m	IIb	C	PS, AZA, IvIG
13/f	12a	14	IIb	PS	15 y 6 m	IIa	B	PS
14/f	13y 5m	14 y m	IIb	PS, ST	14 y 9 m	0	B	PS
15/f	9y 4m	10y 7m	III	PS, ST, AZA, IvIG	l1y 1 m	IIa	B	PS, AZA, IvIG
16/f	14 y	14 y 2m	III	PS, ST, AZA, IvIG	14 y 9 m	IIa	B	PS, AZA
17/f	15 y 5m	15 y 7m	IV	PS, ST, AZA, CSA, IvIG, PP	15 y 9 m	II b	B	PS, MMF, IA

Nr. = Number, f – female, m – male, y=year, m =months,Tx – Thymectomy,

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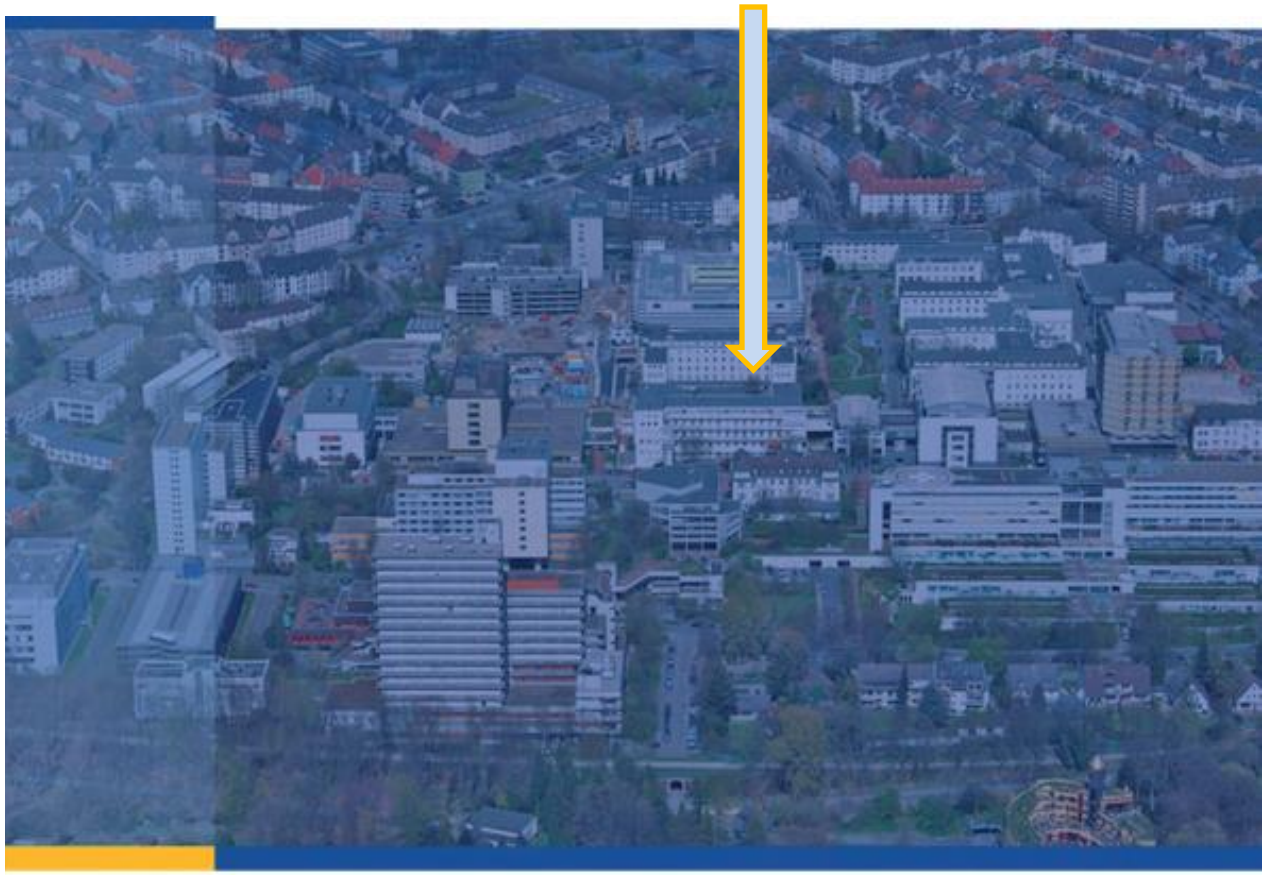
Follow up thymectomy (17 patients)

- follow up: 6 months - 4 years
- remission:
  - grade 0: 5 patients (4 no medication)
  - grade Ia: 4 patients (with medication)
- early thymectomy (< 2 years after onset):
  - 10 patients
  - duration steroid therapy: 1-8 months
- late thymectomy:
  - 7 patients
  - duration steroid therapy: (0)6 – 48 months

Take Home....

- In children and adolescents, early therapy and thymectomy seem to have positive influence on the outcome in JMG with generalised symptoms.
- Early thymectomy led to a shortened period of immunotherapy (in particular corticosteroids) and their possible side-effects on the growing organism.
- Videoscopic thymectomy seems to be as effective as transsternal surgical approach in JMG.
- A national registry will be helpful to collect important data concerning applied therapy/effect of early thymectomy; this will be the basic platform for further development of the therapeutic management in this age group.

Thank you!



Patients and their families

Referring clinicians

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EZSE Essener Zentrum für Seltene Erkrankungen

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