JUVENILE MYASTHENIA GRAVIS

Prevalence and management

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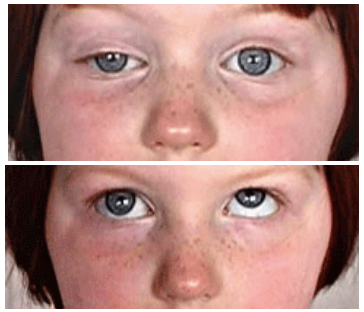
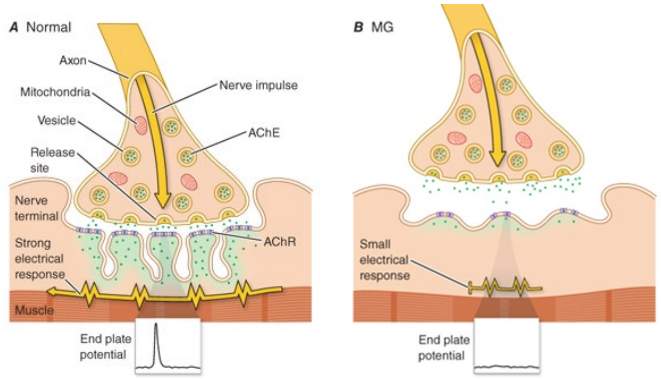
MYASTHENIA IN CHILDREN



MYASTHENIA

- MUSCLE WEAKNESS
- FATIGUABILITY
- FLUCTUATION

Due to impaired neuromuscular transmission



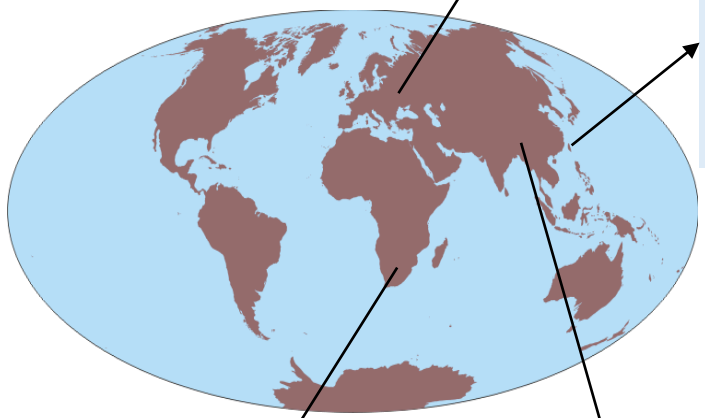
1. JUVENILE MYASTHENIA GRAVIS – MG with symptoms in children younger than 18 yoa
2. CONGENITAL MYASTHENIC SYNDROMES
3. NEONATAL MYASTHENIA/FETAL ACHR INACTIVATION SYNDROME (FARIS)
4. LAMBERT EATON MYASTHENIC SYNDROME

JUVENIL MYASTHENIA GRAVIS
INSIDENCE RATES

MG 4,1-30/1 mill
JMG (0-19 yrs) 1,0-5,0/ 1mill
McGrogan, 2010

MG 7,2-16,0/1 mill
Heldal, Andersen
JMG (0-17 yrs) **1,6**/1 mill
JMG (0-12 yrs) **0,9**/1 mill
Popperud et al 2017

Europe: 10-15% juvenile onset
Evoli 1990



Taiwan:
JMG (0-4 yrs) **8.9**/1 mill
Lai 2010

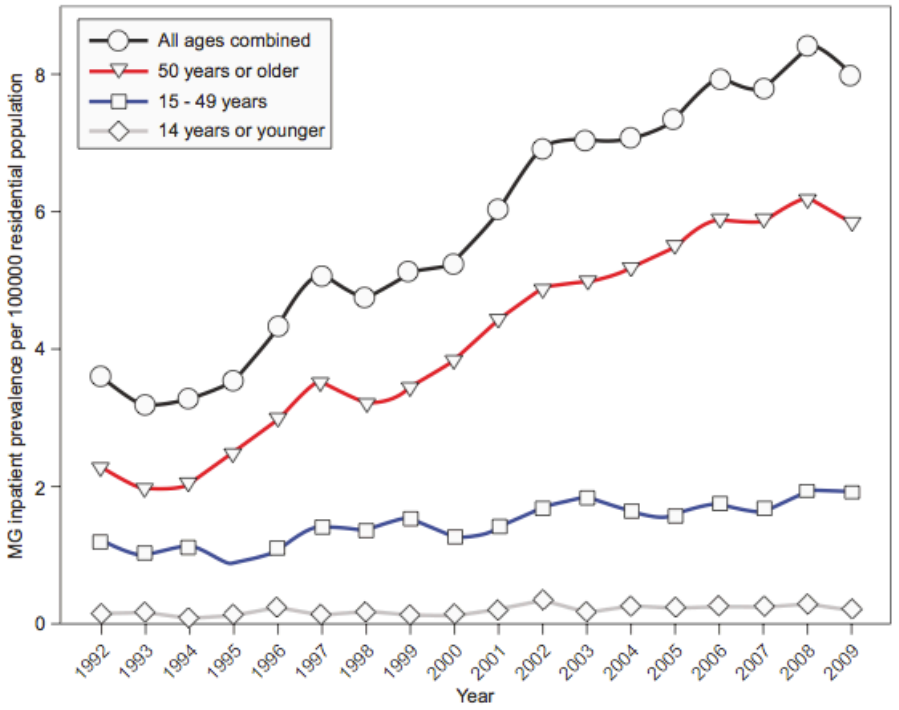
JMG (0-17 yrs) **1,5**/1 mill
Parr, 2014

MG 9,2/ 1 mill
JMG (0-9 yrs) **0,3**/1 mill
JMG (10-19 yrs) 2,2/1 mill
Pedersen, 2013

South-Africa:
JMG (0-10 yrs) **3.3**/1 mill
JMG (10-14 yrs) **2.9**/1 mill

China: 27-50% juvenile onset
Zhang 2007, Huang 2013

JUVENILE MYASTHENIA GRAVIS
INCREASING INSIDENCE?

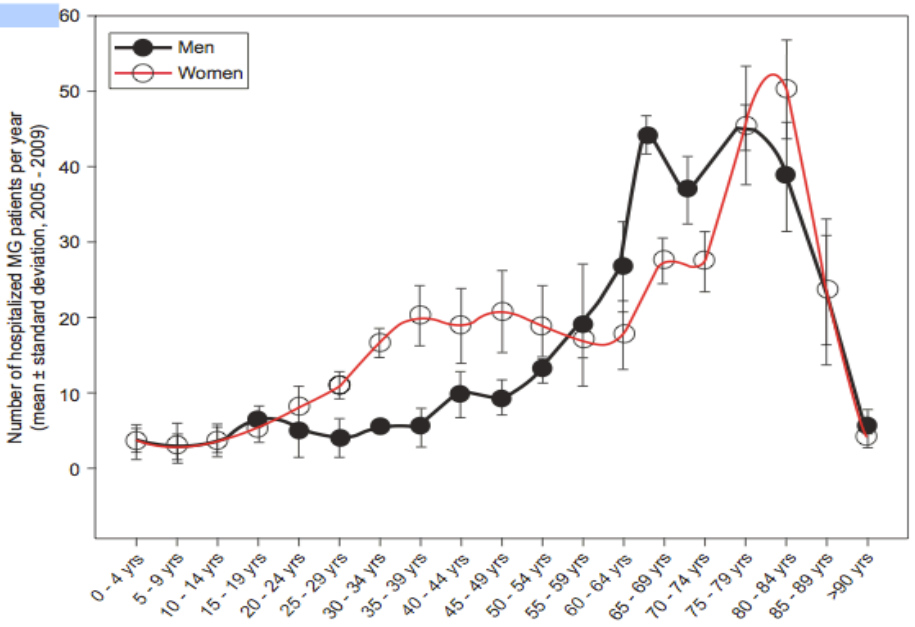


Cetin, 2009

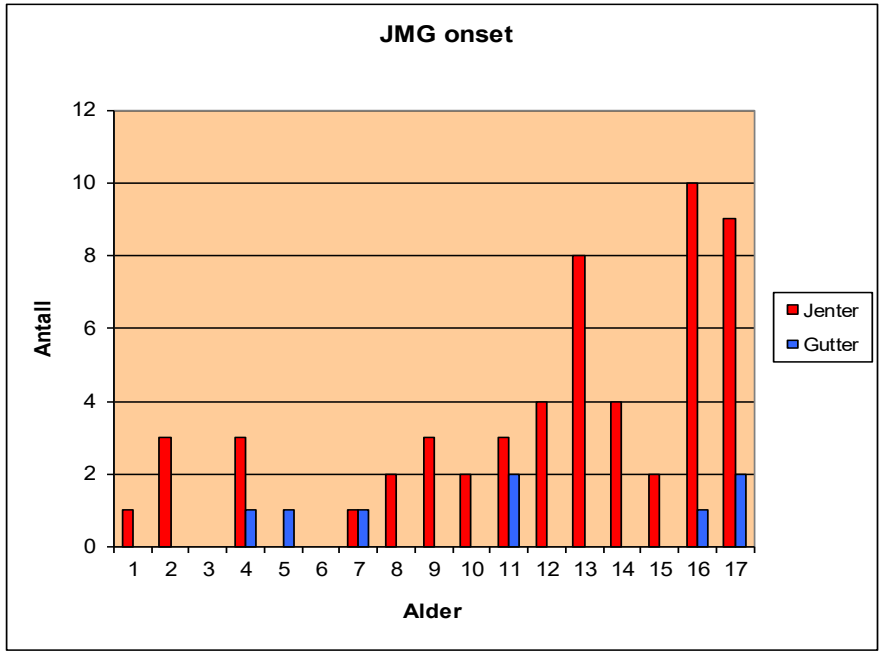
Incidence	JMG < 18 yrs			
Period	N	Person-yrs x10^6	Cases pr mill	**(95% CI)**
1989-93	7	0.98	1.4	**(0.6-2.8)**
1994-98	7	1.02	1.4	**(0.6-2.7)**
1999-03	10	1.06	1.9	**(1.0-3.4)**
2004-08	9	1.1	1.6	**(0.8-3.0)**
2009-13	9	1.12	1.6	**(0.8-3.0)**
1989-13 Females	36	0.51	2.8	**(2.0-3.8)**
1989-13 Males	6	0.54	0.4	**(0.2-0.9**
1989-13 Total	**42**	**1.05**	**1.6**	**(1.2-2.1)**

Age and gender specific incidence of juvenile myasthenia gravis (JMG) in Norway 1989-2013 stratified in five-year periods.
Incidence per million person-years with 95% confidence interval (CI).

JUVENILE MYASTHENIA GRAVIS
GENDER DISTRIBUTION

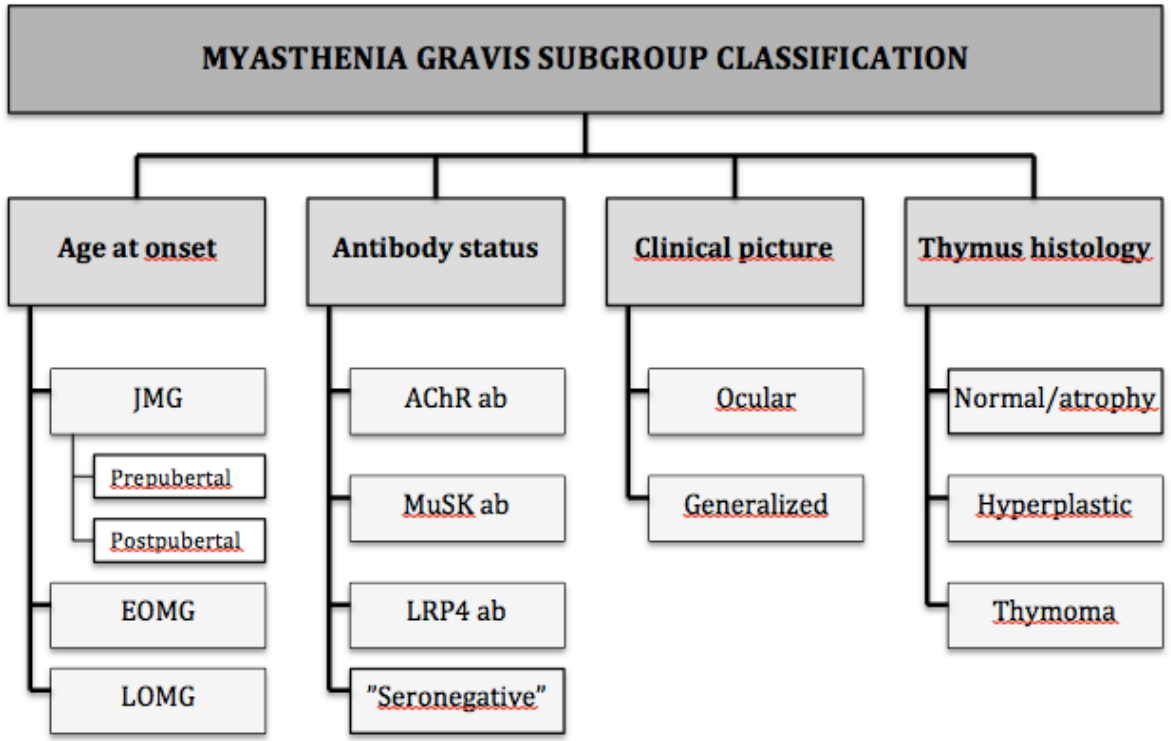


Austria.
Cetin, 2009



JMG in Norway.
Age at onset and gender distribution

MYASTHENIA GRAVIS
SUBGROUP CLASSIFICATION



JUVENILE MYASTHENIA GRAVIS

- AChR ab most common followed by MuSK ab
- OMG more common
- Thymoma rare
- Prepubertal JMG milder disease
- Higher rate of spontaneous remission
- Broader differential diagnoses

JUVENILE MYASTHENIA GRAVIS IN NORWAY

CLINICAL CHARACTERISTICS

	PREPUBERTAL (onset <12), N=21	POSTPUBERTAL (onset ≥12, N=42
Gender, **M:F** (M%, F%)	1:2.5 (29%, 71%)	1:9.5 (10%, 90%)
Onset age in years, median (IQR)	7 (4-10)	16 (12-18)
Caucascian, N (%)	21 (100%)	37 (90%)
Ocular MG, N (%), M:F	3 (14%), 2:1	3 (7%), 2:1
Generalized MG, N (%) • At onset • During first 2 years	18 (86%) • 8 (38%) • 8 (38%)	39 (93%) • 18 (43%) • 19 (45%)
Myasthenic crisis	4 (19%)	2 (5%)
AChR ab positive, N (%) MuSK ab pos, N (%)	12 (57%) 1 (4.8%)	**35 (83%)***
Follow up in years, median (IQR)	27 (11-39)	13 (7-34)
Thymus hyperplasia	7/13 (54%)	23/37 (62%)

* P < 0.05

Oslo University Hospital

Popperud et al 2017

Characteristics of JMG by race/geographical area

References	Region		Pre-pubertal MG			Post-pubertal MG			JMG
		N	AAO (%)	AChR+	OMG	AAO (%)	AChR+	OMG	Thymoma
Asian and Indian ancestry juveniles									
Murai et al. (4)	Japan	268	<10	≈50%	62–81%	NR	NR	NR	4–10%
Gui et al. (5)	China	424*	≤10 (86%)	≈70%	≈95%	10–14 (14%)	≈70%	≈95%	17%
Feng et al. (6)	China South	130	<10	58%	NR	10–19	42%	NR	NR
Lee et al. (7)	South Korea	88	<12 (74%)	90%	97%	12–18 (26%)	87%	70%	NR
Wang et al. (8)	China North	302	<5 (50%)	NR	73%	5–15 (≈50%)	NR	66%	NR
Cohorts with >40% African ancestry juveniles									
Xu et al. (9)	USA (Texas)	60	<10 (40%)	NR	58%	10–17 (60%)	NR	14%	NR
Barraud et al. (10)	France	40	<12 (48%)	58%	37%	12–18 (52%)	NR	24%	2%
Heckmann et al. (11)	South Africa	190	<12 (41%)	56%	43%	12–20 (69%)	NR	NR	1–3%
Cohorts with >45% European ancestry juveniles									
VanderPluym et al. (12)	Canada**	49	≤12 (80%)	52%	46%	13–17 (20%)	≈90%	0	NR
Evoli et al. (13)	Italy	19	<10	74%	26%	NR	NR	NR	0%
Popperud et al. (14)	Norway	63	<12 (33%)	57%	14%#	12–18 (67%)	83%	12%	0%
Jastrzebska et al. (15)	Poland	101	<12 (15%)	71%	NR	12–18 (85%)	94%	NR	1%
Juvenile MG									
Wong et al. (16)	Hong Kong	101	–	–	–	<16	ND	71%	8%
Chou et al. (17)	Taiwan	54	–	–	–	<20	57%	78%	2%
Ashraf et al. (18)	India	77	–	–	–	<15	##	27%	1%
Mansukhani et al. (19)	USA	217	–	–	–	<19	83%	23%	0%
Vecchio et al. (20)	UK	74	–	–	–	<16	84%	51%	NR

Heckmann et al 2022

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

No formal internationally accepted standards of care for JMG

- SUPPORTIVE
- SYMPTOMATIC
- IMMUNOSUPPRESSIVE
- THYMECTOMY

1. 242 ENMC International Workshop: Diagnosis and management of juvenile myasthenia gravis, March 2019. *Munot et al, Neuromuscular Disorders 2020*

2. *O´Connell et al, Managemnet of Juvenile Myasthenia Gravis 2020*

3. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology 2016, Sanders et al*

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

- SUPPORTIVE
- SYMPTOMATIC
- IMMUNOSUPPRESSIVE
- THYMECTOMY

Spontaneous remission occurs in 10% of JMG

Arroyo et al 2022

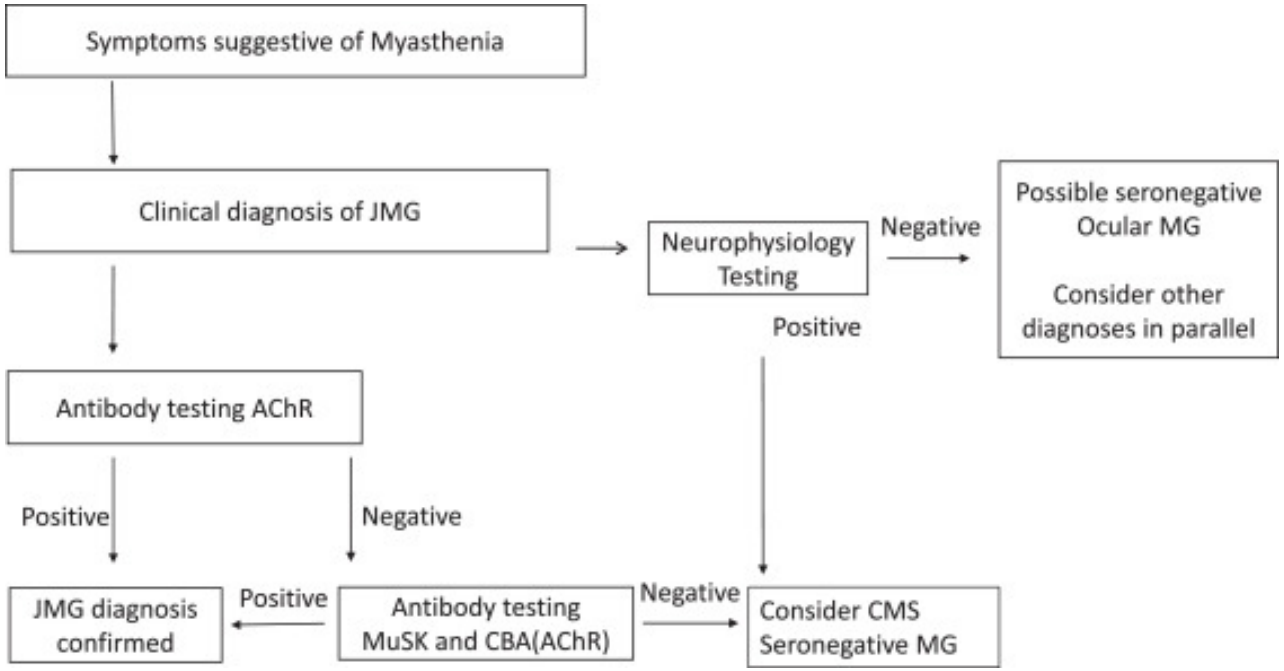
- SR was more common in patients with mild to moderate JMG
- SR was only found in those with no evidence of thyroid disease

Broader differential diagnosis

- CMS, congenital myopathies, mithocondriopathies, brainstem encephalitis, Miller Fisher

JUVENILE MYASTHENIA GRAVIS
DIAGNOSTIC PATHWAY

Important to consider differential diagnoses, especially in seronegative patients

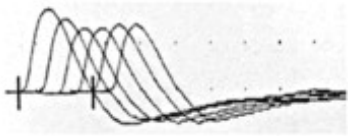


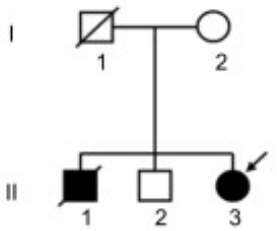
Munot, Robb, Nicks, Palace et al 2020

1st step: how to make the diagnosis?

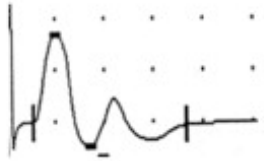
Phenotype | EMG | Family history

- **myasthenic syndrome**
  - weakness and/or fatigability of limbs and oculobulbar muscle
  - variability (short and long term)
  - neuromuscular block
    - Not only distal but also proximal muscles
    - long duration stimulation
  - response to anticholinesterases





- **congenital origin**
  - early onset (since neonatal period)
  - family history
  - absence of anti-AChR and anti-MuSK antibodies
  - peculiar EMG pattern: repetitive response



Bruno Eymard, Daniel Hantaï, Brigitte Estournet, Handbook of Clinical Neurology, Volume 113, 2013, 1469–1480

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

- SUPPORTIVE
- SYMPTOMATIC
- IMMUNOSUPPRESSIVE
- THYMECTOMY

Physical activity
- Low-/intermediate intensity w/rest

Avoid excessive weight gain
- Diet and lifestyle

Treat infections early

Physiotherapy

Speech/Occupational therapy/School

Psychological impact (early recognition)

Respiratory support

Vaccination (varicella, influenza)

Avoid medication that may worsen MG

Ophtalmologist

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

- SUPPORTIVE
- SYMPTOMATIC
- IMMUNOSUPPRESSIVE
- THYMECTOMY

Cholinesterase inhibitors

- 0.5-1 mg/kg every 4-6 h
- maximal daily dose 300-450mg
- adjust to activity/need, 30-60 min before physical activity or meals

- MuSK JMG less responsive, more side effects

- Ptosis>diplopia

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

- SUPPORTIVE
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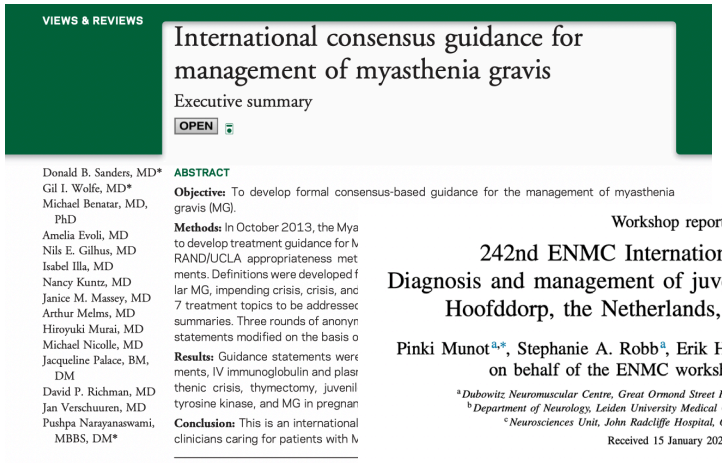
- THYMECTOMY



VIEWS & REVIEWS

International consensus guidance for management of myasthenia gravis

Executive summary

OPEN

Donald B. Sanders, MD*
Gil I. Wolfe, MD*
Michael Benatar, MD, PhD
Amelia Evoli, MD
Nils E. Gilhus, MD
Isabel Illa, MD
Nancy Kuntz, MD
Janice M. Massey, MD
Arthur Melms, MD
Hiroyuki Murai, MD
Michael Nicolle, MD
Jacqueline Palace, BM, DM
David P. Richman, MD
Jan Verschuuren, MD
Pushpa Narayanaswami, MBBS, DM*

ABSTRACT

Objective: To develop formal consensus-based guidance for the management of myasthenia gravis (MG).

Methods: In October 2013, the Mya
to develop treatment guidance for M
RAND/UCLA appropriateness met
ments. Definitions were developed f
lar MG, impending crisis, crisis, and
7 treatment topics to be addressed
summaries. Three rounds of anonyn
statements modified on the basis o

Results: Guidance statements were
ments, IV immunoglobulin and plasr
thenic crisis, thymectomy, juvenil
tyrosine kinase, and MG in pregnan

Conclusion: This is an international
clinicians caring for patients with M

Workshop report

242nd ENMC International Workshop: Diagnosis and management of juvenile myasthenia gravis Hoofddorp, the Netherlands, 1–3 March 2019

Pinki Munot[a,*], Stephanie A. Robb[a], Erik H. Niks[b], Jacqueline Palace[c], on behalf of the ENMC workshop study group[1]

[a] Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London, United Kingdom
[b] Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands
[c] Neurosciences Unit, John Radcliffe Hospital, Oxford, United Kingdom

Received 15 January 2020

Management of Juvenile Myasthenia Gravis

Karen O'Connell[1], Sithara Ramdas[2] and Jacqueline Palace[1]*

[1] Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom,
[2] Department of Paediatric Neurology, John Radcliffe Hospital, Oxford, United Kingdom

First line: **Steroids**

- 0,5 mg/ kg alternate days gradually uptitrated to maximum 1.5 mg/kg (max 100 mg) alternate days or 1 mg/kg (max 60 mg) daily *(5 mg alternate days uptitrated with 5 mg every 5th day)*

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

- SUPPORTIVE
- SYMPTOMATIC
- IMMUNOSUPPRESSIVE
- THYMECTOMY

Second line:

1. When no response to steroids
2. Inability to wean steroids to reasonable dose
3. Intolerable side effects to steroids

- Azathioprine/Mycophenolate mofetil
- Cyclosporin/methotrexate
  - to little data/experience in JMG
- Cyclophosphamide
  - side effects, malignancy and fertility

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

Rituximab in juvenile myasthenia gravis-an international cohort study and literature review

Sithara Ramdas [a,b,*], Adela Della Marina [c], Monique M. Ryan [d], Kenneth McWilliam [e], Andrea Klein [f,g], David Jacquier [h], Setareh Alabaf [i], Anne-Marie Childs [j], Deepak Parasuraman [k], David Beeson [l], Jacqueline Palace [i], Heinz Jungbluth [m,n]

- SUPPORTIVE
- SYMPTOMATIC
- IMMUNOSUPPRESSIVE
- THYMECTOMY

Second line:

- Rituximab
  - Remission rate (CR/PR) of 60% and significant morbidity reduction with reduced hospital/intensive care admission.
  - 10 JMG, 5.9-15.8 yoa
  - 24 months observation
  - 20 JMG cases from 11 publications, 35% CR/PR

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

- SUPPORTIVE
- SYMPTOMATIC
- IMMUNOSUPPRESSIVE
- THYMECTOMY

IVIg

- Acute exacerberations, preop
- Refractory JMG

PLEX

- Acute exacerberations, preop
- Refractory JMG
- Might be more effective than IVIg *(Liew 2014)*

C5 inhibitors

- Adults
- High cost

JUVENILE MYASTHENIA GRAVIS
MANAGEMENT

- SUPPORTIVE
- SYMPTOMATIC
- IMMUNOSUPPRESSIVE
- THYMECTOMY

ELSEVIER
Neuromuscular Disorders 31 (2021) 1113–1124
www.elsevier.com/locate/nmd

Review

Effectiveness of thymectomy in juvenile myasthenia gravis and clinical characteristics associated with better outcomes

Wei Chin Ng[a,*], Louise Hartley[b]

[a] Barts and The London School of Medicine and Dentistry, Whitechapel, London E1 2AD, United Kingdom
[b] Department of Paediatric Neurology, The Royal London Hospital, London E1 1BB, United Kingdom

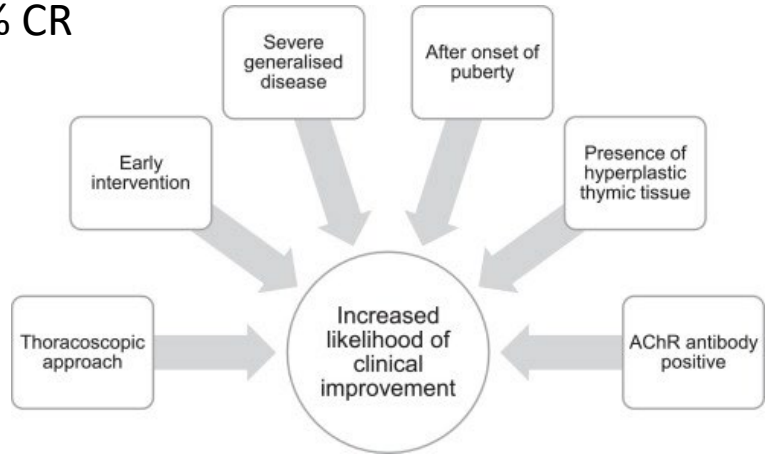
Received 4 May 2021; received in revised form 5 September 2021; accepted 30 September 2021

- No RCT in JMG
- Thymic imaging in all (CT or MRI)

  Thymoma absolute indication

Systematic review *(Ng et al 2021)*

- 588 JMG thymectomies
- 77% improved, 40% CR

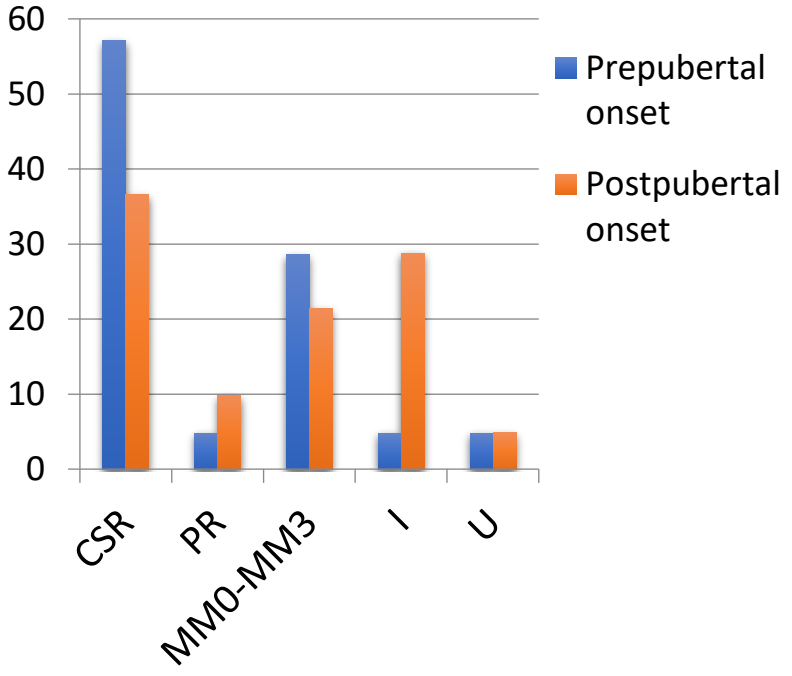


JUVENILE MYASTHENIA GRAVIS IN NORWAY

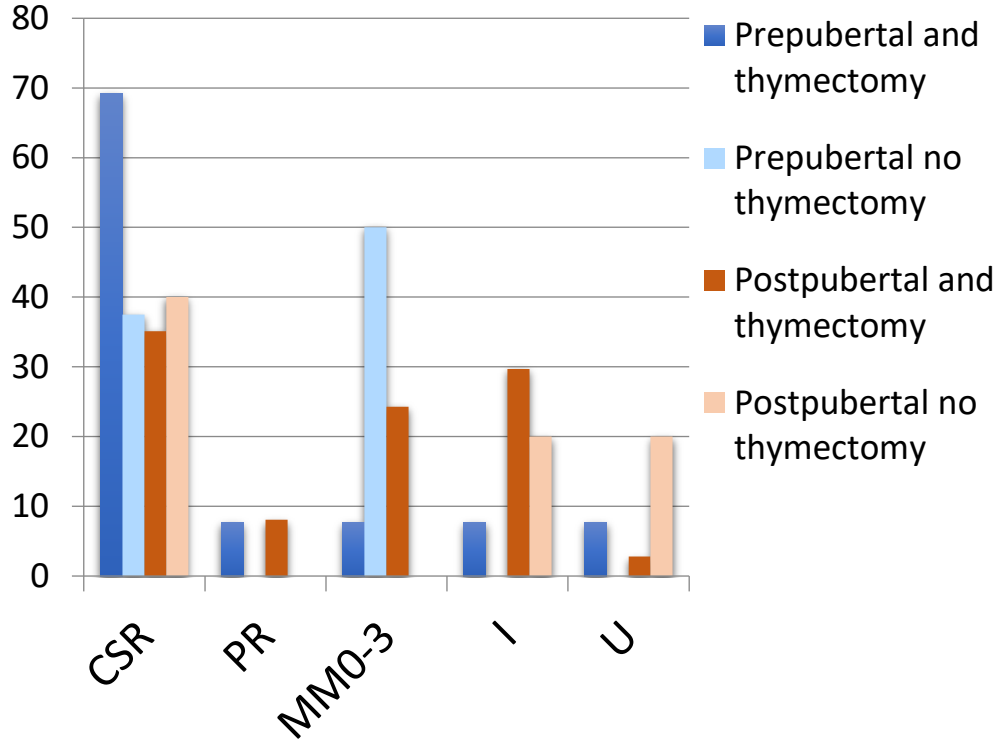
TREATMENT

	PREPUBERTAL, N=21	POSTPUBERTAL, N=42
Pyridostigmine po, N (%)	21 (100%)	42 (100%)
Pred po, N (%)	**6 (29%)**	**20 (48%)**
Aza/Cic/MyM, N (%)	2 (10%)	**15 (36%)***
IVIG, N (%)	**5 (24%)**	**15 (36%)**
Plasma, N (%)	9 (43%)	9 (21%)
Thymectomy, N (%) • **AChR ab positiv**	**13 (62%)** • **10 (77%)**	**37 (88%)*** • **33 (89%)**
Thymus histology • Hyperplasia, N (%) • Normal, N (%) • Thymoma, N (%) • Unknown, N (%)	 7 (54%) 3 (23%) 0 3 (23%)	 23 (62%) 9 (25%) 0 5 (14%)
Time from onset to thymectomy in years, median (IQR)	**2 (1.2-3.7)**	**1.3 (0.8-2.2)**
Medication last follow up • None, N (%) • Pyridostig, N (%) • Pred po, N (%) • Aza/Cic/MyM, N (%) • Plasma/IVIG, N (%)	 14 (67%) 5 (24%) 2 (10%) 2 (10%) 1 (4.8%)	 17(41%) 19 (46%) **15 (37%)*** 11 (27%) 1 (2.4%)

JUVENILE MYASTHENIA GRAVIS IN NORWAY
POST TREATMENT OUTCOME



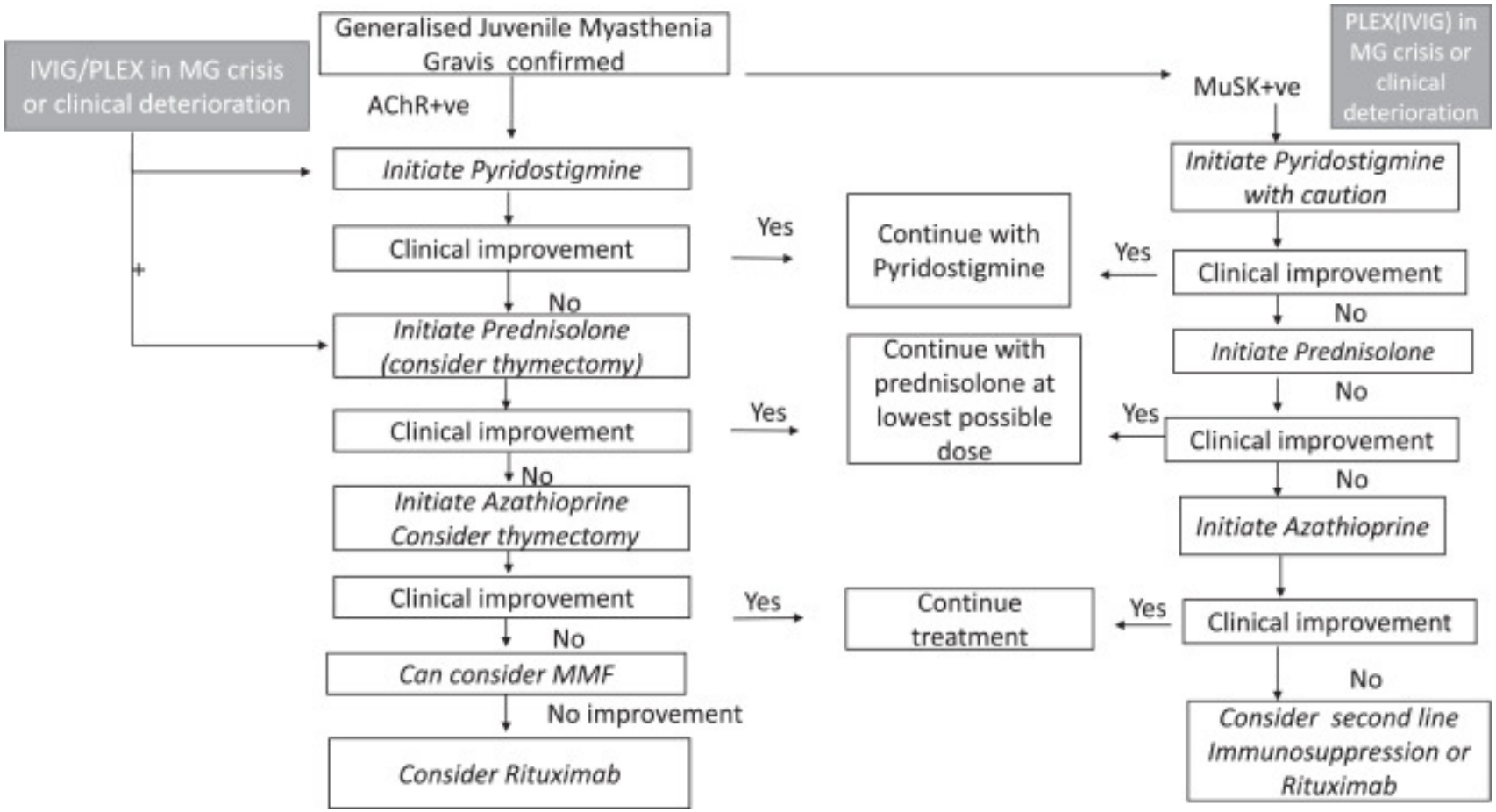
Clinical outcome after treatment in prepubertal vs postpubertal onset group. Proportion of patients in % in each MGFA Postintervention Status category.



Clinical outcome in prepubertal and postpubertal onset group stratified by thymectomy status. Proportion of patients in % in each MGFA Postintervention Status category.

TREATMENT PATHWAY

AChR and MuSK JMG



+ Supportive therapy

Munot, Robb, Nicks, Palace et al 2020

Conclusions

- JMG is rare with race/geographical variation
- Early diagnosis and treatment is important to prevent disability/morbidity incl permanent eye movement impairment/amblyopia
- Management is multidisiplinary and include symptomatic and immunosuppressives based on experience in adult MG
- Thymectomy when thymoma, postpubertal AChRab generalized JMG, individual assessment in prepubertal JMG