

## ARTICLE



# Demographics and ocular findings in children with myasthenia

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**PURPOSE:** To report the demographics and ocular features of myasthenia gravis in the paediatric population.**METHODS:** Retrospective revision of the medical records of all patients younger than 18 years of age with myasthenia who were examined at Great Ormond Street Hospital between the 1st of January 2016 and 1st of January 2020.**RESULTS:** A total of 49 children were assessed during the 4-year period. There was a female predominance, with only 12 males (24.5%). 26 children (53.1%) had juvenile myasthenia gravis (JMG) while 18 (36.7%) had congenital myasthenic syndrome (CMS). 4 patients (8.2%) were diagnosed with probable CMS while 1 (2.0%) was classified as probable JMG. The mean age at diagnosis was 5.3 years old (SD 3.9) whereas the mean age at onset was 3.7 years old (SD 3.9). Almost half of the children (49%) had ocular involvement, present in 19 patients in the JMG group (70.4%) and in 5 children (22.7%) in the CMS cohort. Ptosis was the most common sign at presentation, seen in 32 patients (65.3%). Nine patients (18.4%) presented with a squint and another 7 (14.3%) developed it later on. Anti-acetylcholine receptor antibodies were positive in 18 of the 26 JMG patients (69.2%) whereas identifiable mutations were found in the 18 CMS patients (100%). Pyridostigmine was the drug of choice in our series, used by thirty-three patients (67.3%). The majority of the patients (73.5%) improved after treatment.**CONCLUSIONS:** JMG was the most common type of paediatric MG, specifically the ocular form. Ptosis was the most common sign at presentation. The majority of the patients improved after medical treatment.*Eye* (2023) 37:700–704; <https://doi.org/10.1038/s41433-022-02030-5>

## INTRODUCTION

Myasthenia in children can be inherited or acquired. Myasthenia gravis is a chronic autoimmune disorder affecting the neuromuscular junction characterised by weakness of the voluntary muscles of the body [1] caused by autoantibodies directed against the postsynaptic membrane of the neuromuscular junction [2]. The extraocular muscles and levator palpebrae tend to be involved. When the onset of the condition is prior to 18 years of age, the term juvenile myasthenia is applied. Neonatal myasthenia gravis (NMG) is a transient disorder present at birth due to passive transfer of antibodies from a mother who has autoimmune MG.

Congenital myasthenic syndrome (CMS) is a group of inherited conditions caused by mutations in genes involved in the structure or function of the neuromuscular junction (NMJ). Typically, the muscle weakness is present at birth, but it can appear in later childhood, adolescence or adults.

A patient with fatigable ptosis and/or ophthalmoplegia present at birth or early life should raise the possibility of congenital myasthenic syndrome.

In autoimmune forms, there are two main types of presentations. Ocular MG is defined when exclusively the extraocular muscles and levator palpebrae are involved and it accounts for 10–35% of paediatric myasthenic patients [3]. Generalised myasthenia accounts for the remaining 65–90% and is diagnosed when nonophthalmic weakness is observed, with or without eye involvement.

Although adult MG has been studied in large populations, little is known about the paediatric forms. The aim of our study is to characterise the demographics and ocular manifestations in children with myasthenia.

## MATERIALS AND METHODS

The medical records of 49 patients younger than 18 years old with any type of myasthenia gravis who presented between January 2016 and January 2020 were retrospectively reviewed. Search terms included myasthenia gravis (ocular and generalised), neonatal myasthenia gravis, congenital myasthenia gravis and juvenile myasthenia gravis in the EPIC-based electronic health records searching tool.

CMS diagnosis was based on clinical symptomatology at birth or early life plus either molecular genetic testing involving the CMS genes or neuromuscular junction transmission abnormalities on electrophysiology studies. The term probable CMS was applied when no supportive testing had been reached but the clinical picture was consistent with a CMS diagnosis.

JMG was diagnosed according to the clinical features of MG in addition to at least one of the following: positive antibodies anti-acetylcholine receptors (AChR-ab), positive antibodies against muscle-specific kinase (MuSK-ab), positive neurophysiology and/or response to treatment. The term probable JMG was used when supporting test were negative or unknown.

When only ocular involvement was observed, patients were classified as ocular MG whereas patients with respiratory or swallowing involvement alone were classified as bulbar MG. The rest of the patients with limb and/or facial weakness were classified as generalised MG.

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The diagnosis was made by a neurologist or by an ophthalmologist. Data regarding demographics including sex, ethnicity, age at onset, age at diagnosis, history of prematurity, history of consanguinity, family history of MG, symptoms at onset, form of MG, involvement, clinical investigations, outcomes and thymectomy performed were collected. Ophthalmology reports including visual acuity, ptosis or strabismus at presentation, strabismus later on, ptosis laterality and limitation of extraocular movement were reviewed separately when available.

Response to treatment was graded using a similar method to that of Mansukhani et al. [2] and was divided into 6 categories: remission was achieved when the patient was asymptomatic, and could be either complete if the patient had been off treatment for at least one year or pharmacologic if the patient was still on treatment; improvement was applied when symptoms had improved with treatment; unchanged was defined when no changes had been found with treatment; worsening was applied when symptoms worsened despite appropriate treatment from clinical history recorded in the notes according to parents and/or children. The last category was untreated and was applied to those patients whose symptoms were so mild they never received any treatment.

## RESULTS

Forty-nine patients with MG were seen in Ophthalmology and/or Neurology during the 4-year study period. Demographic characteristics of the study group are summarised in Table 1. Twenty-six patients (53.1%) had JMG and 18 (36.7%) had CMS. Four patients (8.2%) were diagnosed with probable CMS as results of molecular genetic testing were still pending by the end of the study period and 1 patient (2.0%) was classified as probable JMG as had been referred for a second gastroenterology opinion and supportive testing were unknown.

The gender distribution was thirty-seven females (75.5%) and twelve males (24.5%). Among the twenty-two children in the CMS group there were sixteen females (72.7%) whereas twenty-one of the twenty-seven patients in the JMG group were females (77.8%). There was no statistically significant difference between the two groups ( $p > 0.1$ ), with a similar female preponderance in both.

Eighteen patients (36.7%) were White caucasian, ten (20.4%) were Afro-Caribbean and nine children (18.4%) were Asian. Nine out of the ten Afro-Caribbean patients had JMG, whereas seven out of the nine Asian children had CMS. Three (6.1%) had a mixed ethnicity while nine (18.4%) patients' ethnicities were either unknown or classified as other ethnic group.

The mean age at onset was 3.7 years old (SD 3.9) whereas the mean age at diagnosis was 5.3 years old (SD 3.9). Eight patients (16.3%) were premature. Ten patients (20.4%) had a history of consanguinity and only one (2.0%) had a positive family history of MG.

In the CMS group, ten children (45.5%) presented with generalised weakness, whereas seven (31.8%) had bulbar weakness and five had ocular signs (22.7%). On the contrary, in the JMG group, ocular form was the most frequent, present in nineteen patients (70.4%), whereas six had the generalised form (22.2%) and two had bulbar MG diagnosis (7.4%).

Ocular symptoms were the most common form of presentation (69.4%), present in twenty-five and nine patients in the JMG and CMS cohort, respectively.

Generalised and bulbar symptoms were more frequent in the CMS cohort, and these children usually presented with more than one symptom. Swallowing or feeding difficulties were present in ten patients (20.4%) whereas respiratory difficulties were found in eight patients (16.3%). Hypotonia was present in eight patients (16.3%) while walking difficulties was found in six patients (12.2%). Six patients (12.2%) had stridor at onset. Facial weakness was present in five patients (10.2%) at presentation.

Of the thirty-four patients with ocular symptoms at presentation, twelve (35.3%) presented with ptosis accompanied by limitation of extraocular movements or squint. Ptosis alone was found in nine patients (26.5%) at presentation whereas ptosis with

**Table 1.** Demographic characteristics of the study group.

	CMS (n = 22)	JMG (n = 27)	Total (n = 49)
<b>Sex</b>			
Female	16	21	37
Male	6	6	12
<b>Ethnicity</b>			
White	10	8	18
Asian	7	2	9
Black	1	9	10
Mixed background	0	3	3
Other ethnic group/unknown	4	5	9
<b>Mean age (years)</b>			
At onset	0.69	5.95	3.73
At diagnosis	3.63	6.37	5.33
<b>Ocular symptoms at onset</b>			
Ptosis	2	7	9
Squint	0	2	2
Diplopia + ptosis	0	2	2
Ptosis + ophthalmoparesis or squint	3	9	12
Ptosis + non-ocular symptoms	4	5	9
<b>Bulbar/generalised symptoms at onset</b>			
Respiratory difficulties	8	0	8
Swallowing difficulties	9	1	10
Stridor	6	0	6
Hypotonia	8	0	8
Facial weakness	1	4	5
Walking difficulties	3	3	6
<b>Involvement</b>			
Ocular	5	19	24
Bulbar	7	2	9
Generalised	10	6	16
Consanguinity	9	1	10
Prematurity	2	6	8
Family history of MG	1	0	1
<b>Ptosis</b>			
At presentation	10	22	32
At the end of study period	19	22	41
Bilateral	18	19	37
Unilateral	1	3	4
<b>Squint</b>			
At onset	2	7	9
During study period	2	5	7
Amblyopia	0	5	5
Limitation of EOM	13	14	27
<b>Type of Limitation</b>			
Upgaze paresis	7	7	14
Abduction deficit	2	9	11
Adduction deficit	0	2	2
Downgaze paresis	2	0	2
Limitation in all directions of gaze	2	3	5
Nonspecific ophthalmoplegia	3	0	3

diplopia was found in 2 patients (5.9%). Squint alone was only present in two patients (5.9%). Nine patients (26.5%) presented with ptosis associated with other bulbar or generalised symptoms.

Over the 4-year study period, ptosis was seen in forty-one patients (83.7%). Ptosis was present at onset in thirty-two children (65.3%). It was bilateral in the vast majority of the patients (90.2%).

Nearly half of our cohort (46.3%) noticed a significant improvement with medical treatment. Interestingly, none of our patients experienced any worsening and none of them required surgical treatment for ptosis.

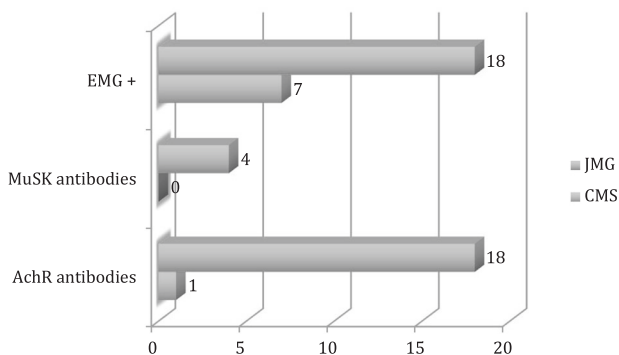
Sixteen patients (32.7%) had a squint: nine of those had the squint at presentation (56.3%) whereas the remaining seven (43.8%) developed it afterwards. Four of them (25.0%) required squint surgery. Exotropia was the most common type, present in fourteen patients (87.5%). Twelve patients (24.5%) were followed up locally, so no further ophthalmology data was available for them.

Amblyopia was only diagnosed in five patients (10.2%) and was refractive in two patients and strabismic in the remaining three. However, twenty patients (40.8%) were only seen by the Neurology team and visual acuity was not formally assessed. Stereoacuity was assessed in sixteen patients and fourteen of them (87.5%) demonstrated good stereopsis.

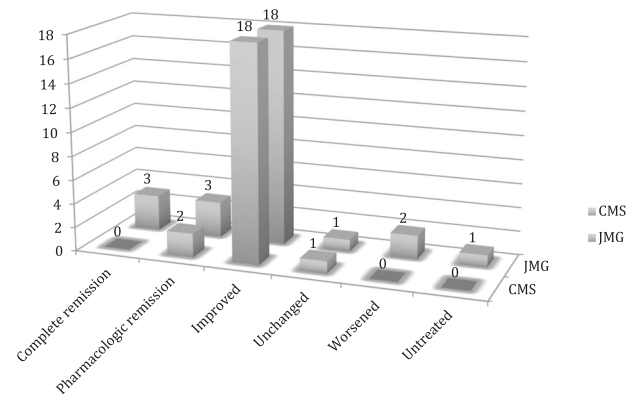
Twenty-seven patients (55.1%) had limitation of extraocular movements. The most common was upgaze paresis, present in fourteen patients (28.6%), followed by abduction deficit in eleven patients (22.4%). Five patients (10.2%) had limitation in all directions of gaze whereas only two had adduction deficit (4.1%). Downgaze paresis was present in two patients (4.1%). Three patients had a non-specific ophthalmoplegia (6.1%).

Anti-acetylcholine receptors antibodies were positive in eighteen JMG patients (66.7%). Positive antibodies against muscle-specific kinase were found in four JMG patients (14.8%). Electromyography showed either a decrement on repetitive stimulation and/or increased jitter on single fibre in twenty-five patients (51.0%): eighteen in the JMG group (66.7%) and seven in the CMS group (31.8%) (Fig. 1). CMS genes mutations were found in the eighteen confirmed CMS patients (100%): *DOK7* mutation was the most frequent, positive in six patients (33.3%) followed by *CHRNE* mutation present in five patients (27.8%). Three patients (16.7%) had a *CHRNA1* mutation whereas two (11.1%) had a *COLQ* mutation. The last two patients (11.1%) were found to have a mutation in *RAPSN*.

Eight patients (16.3%) were in remission during the 4-year study follow up: five of those (10.2%) were in pharmacologic remission whereas the remaining three (6.1%) were in complete remission. Thirty-six patients (73.5%) improved with treatment whereas two were unchanged (4.1%). Only two patients did not respond to first-line treatment (4.1%) and needed escalation. The last patient was left untreated, as her symptoms were insignificant (2.1%) (Fig. 2). Five patients underwent a thymectomy (10.2%). Treatment choice was determined by the Neurology team. Pyridostigmine was the drug of choice in our cohort, used by thirty-three patients (67.3%). It acts by increasing the number of AChRs activated by a single quantum;



**Fig. 1 Clustered Bar showing immunologic and electrophysiologic testing of the study population.** EMG = electromyography. MuSK antibodies = antibodies against muscle-specific kinase. AchR antibodies = anti-acetylcholine receptors antibodies.



**Fig. 2 3D Clustered columns showing outcomes of the study population.**

thus is the first-line treatment for JMG. Ten patients needed oral steroids (20.4%), the majority of them as adjuvant therapy, whereas twelve (24.5%) were using salbutamol (10 CMS children vs 2 JMG patients). Adrenergic agonists were found to be effective in the CMS caused by mutations in *COLQ* and *DOK-7*. Four CMS patients (8.2%) were treated with 3,4-Diaminopyridine (3,4-DAP), a cholinergic agonist usually used as second-line treatment or in combination.

## DISCUSSION

The European incidence of MG in a recent review has been shown to be 30/1.000.000/year, decreasing to 1-5/1.000.000 in the paediatric population [4]. These data suggest paediatric MG can be classified as a rare disease, affecting <1 in 2000 people, which, along with the lack of large population-based studies, make its diagnosis and treatment a challenge. The aim of our study was to characterise the demographics, ocular symptoms, treatment choice and response to treatment in children with MG.

Our study showed a female preponderance, similar to the reported in a recent epidemiological study from the UK [5]. Caucasian children were more commonly affected in our cohort, which is consistent with the existing American literature [2]. However, some authors [6] have described a greater incidence among African American children.

The mean age at onset in our cohort was 43 months. This is consistent with Kim et al. [7] and Vanikieti et al., who reported a mean age at onset of 38 months and 49 months, respectively.

Evans OB et al. [8] suggested an association with prematurity, revealing up to 55% of the juvenile form with onset before age 3 years had a history of prematurity. In our cohort, prematurity was also more common than in the normal population, with 22.2% of the JMG patients born prematurely.

Consanguinity was not uncommon in our series, occurring approximately in 1 out of 5 patients. This finding has already been described in the literature in association with *COLQ* mutation. Malik et al. described the presence of a mutation in this gene in a Syrian family, where the two affected children were born to first cousin parents [9].

The influence of family history of MG was not observed in this study, as only one patient in our cohort had a positive family history (2.0%). Similar data were described by Mansukhani et al. [2] and by Barraud et al. [10], where only 8.2% and 2.5% had a positive family history of MG.

Ocular involvement was the most common subtype of MG, with ocular symptoms being the most common form of presentation, present in sixty-nine percent of our study population. This finding is similar to Mansukhani et al., who found 75% of their cohort

presenting with ocular features and to Popperud et al. cohort [11], which also showed 69% of ocular symptoms at onset.

Ptosis was the most common ocular sign, present in 83.7% of our paediatric population over the 4-year study period. Barraud et al. [10] and Chou et al. [12] reported a similar prevalence, with ptosis being the most common symptom, present in 78% and 96.4%, respectively. Notably it was bilateral, responded to medical treatment with very low amblyopia rates so caution should be applied to surgical intervention. In our series, none of the patients underwent ptosis repair.

Strabismus is more variable, ranging from 20.7% to 56.0%, depending on the authors [13]. Interestingly, exotropia was the most common form of squint in our population, whereas esotropia was the most common described by other colleagues [2]. Furthermore, we investigated the number of patients who were straight in primary position at onset but developed a squint afterwards and found that seven of them developed a squint later on. Unfortunately, one fourth of our children were followed up locally by the end of our study period so we were unable to assess those.

In the literature, amblyopia has been found in up to 50% of children with ocular MG but was uncommon in our cohort. The reviewed literature confirms it has a very good prognosis in most of the cases, with only 3% of residual amblyopia after appropriate occlusive treatment [3, 13].

Ophthalmoplegia is also very variable, ranging from 1.8% to 53.2% on the existing literature [2, 12, 13]. More than half of the patients in our cohort had some sort of limitation in ocular movements. Up gaze paresis and abduction deficit were the most common types of limitation in our series.

Anti-AChR and anti-MuSK antibodies were positive in 81.5% of our JMG cohort, representing the most common test used to confirm the juvenile form. This is slightly more frequent than other authors. Barraud et al. cohort [10] reported 61% of positive antibodies. Mansukhani et al. [2] found positive antibodies in 70.8% of their patients.

M Kinali et al. reviewed 46 patients with CMS diagnosis. Mutations were identified in 32 of them in 6 different genes. *RAPSN* mutation was the most common followed by *COLQ* mutation. The rest of the patients had mutations in *CHRNE*, *DOK7* and *CHRNA1*. *CHAT* mutation was present in one of their patients whereas this gene was not found in our population [14]. We identified mutations in the remaining 5 genes. However, in our population, the most frequent mutation identified was *DOK7*, followed by *CHRNE*.

The majority of our patients improved with treatment, but only 16% were in remission by the end of the study period. Chou et al and Mansukhani et al found a similar outcome, with improvement in 59.3% and 73.6%, respectively. However, the rate of remission differed from both series being the highest in Mansukhani et al. cohort, but this is probably due to their long term follow up comparing to Chou and colleagues and ours.

As with any retrospective review, our study has some limitations. First, not all of our patients were seen by an ophthalmologist. The patients who were only seen by a neurologist had a limited ophthalmology assessment. Second, a small percentage of the patients were followed up by their local ophthalmologist and we were unable to collect those data to ascertain the number of them who developed a squint later on. Finally, our study period was short, so the remission rate was lower than expected.

## CONCLUSIONS

JMG and specifically the ocular form, was the most common form of presentation among our paediatric myasthenia gravis population. Our findings confirm a female preponderance among these patients. Ptosis was the most common symptom,

present in most of the patients. The majority of the patients improved with appropriate medical treatment.

Larger studies with longer follow up are necessary to improve our knowledge in this rare condition.

## SUMMARY

### What was known before

- We were interested in knowing the demographics, ocular features and outcomes of our MG patients at GOSH so we did an audit of the patients seen in the last 4 years and we decided to write it up as it is an uncommon disease.

### What this study adds

- It helps understanding more about the ocular features in children with myasthenia and also adds that the majority of the patients improved with only medical treatment.

## DATA AVAILABILITY

Data analysed in this study are available in the Great Ormond Street Hospital NHS Foundation Trust Clinical Audit department, reference number 2851.

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## AUTHOR CONTRIBUTIONS

All authors have made a substantial contribution of the manuscript and have approved the final version.

### COMPETING INTERESTS

The authors declare no competing interests.

### ADDITIONAL INFORMATION

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