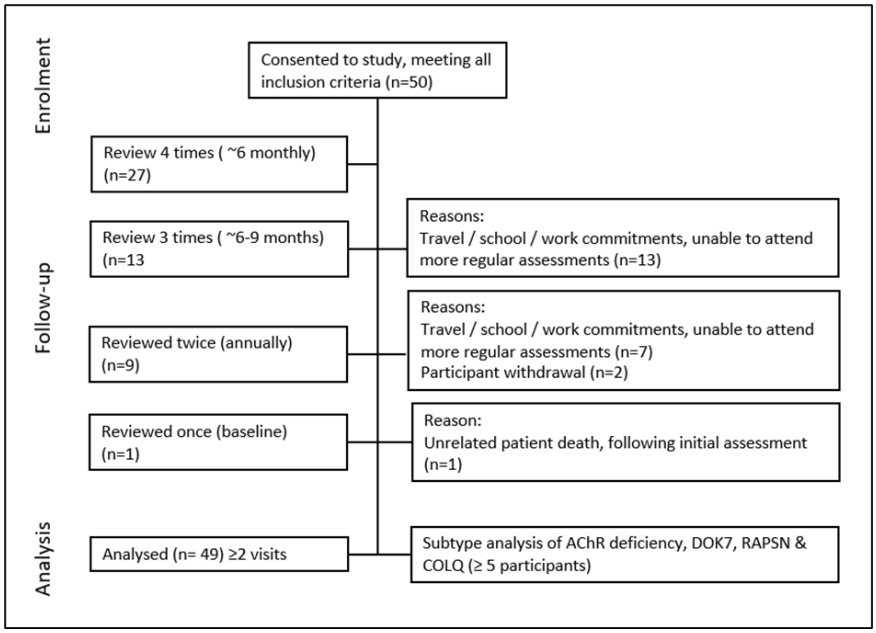
**ISRCTN Registry – basic summary**

**An observational longitudinal study of congenital myasthenic syndromes**

**Background:** Congenital Myasthenic Syndromes (CMS) are a group of rare genetic disorders affecting the neuromuscular junction function. They are characterised by fatigable muscle weakness with onset in most cases in infancy or early childhood. The severity of CMS is variable amongst individuals, fluctuating with physical effort, which can make objective assessments challenging. Currently, there are no validated outcome measures for use in CMS, and most clinicians use outcome measures validated in Myasthenia Gravis and other neuromuscular disorders. There is a need to establish validated outcome measures in CMS with the emerging novel treatments in the pipeline.
Primary aim: to identify relevant and reliable outcome measures for assessing and monitoring change in the CMS population within the UK.
Secondary aims: 1) To collect robust clinical data, informing the natural history of the CMS population, 2) Identify how different CMS phenotypes present on clinical assessment.

**Methods:** A single centre, observational exploratory study of patients with a range of genetically confirmed CMS, of all ages. Study visits were conducted alongside routine patient care, over a 24-month period at 6-12 monthly intervals. Assessment scales used varied depending on the age of the patient, but the aim was to complete all assessments suitable, adopting interchangeable outcome measures at border zones. Those adopted included Quantitative Myasthenia Gravis (QMG) scale, Sit to stand in one minute, Timed 10 metre run, Timed rise to stand, Six-minute walk test, Spirometry, Stair climb and community physical activity monitors. Patient reported outcome measures included the Myasthenia Gravis Activities of Daily Living (MG-ADL), EQ-5D-5L, and Hospital Anxiety and Depression Scale (HADS). A patient self-reported home assessment and the Care giver indirect and informal care cost assessment questionnaire were also used.

**Participant Flow:**



**Results:** 50 participants we recruited to an observational study, which ran from February 2022 until May 2024. All participants had a confirmed genetic diagnosis of CMS. One patient (<2 years of age) was unable complete the assessments and their results are not reported. The remaining 49 patients were seen 2-4 times over a 2-year period for face-to-face evaluations.

**Baseline Characteristics**: Subtypes included AChR-deficiency (n=15), AGRN-DOK7 clustering complex (n=15), RAPSN (n=6), COLQ (n=5), others (n=8). Median age 25.5 years (range 1 – 72), 26 were female. 39 patients presented with ptosis, with a mean of 23.2 seconds before ptosis onset with up gaze. Few participants (26%) presented with dysarthria (mean 45.9 seconds) on at least one assessment. Variability was seen in limb girdle fatigue (shoulders, neck and hips) even amongst participants of the same subtype.

Table 1 outlines the baseline demographics
Figure 1 shows the relative proportions of CMS genetic defects.

| *CMS genetic subtype* | *n* | *Age (years) median (range)* | *Male : Female* |
|---|---|---|---|
| *AChR deficiency** | *15* | *25 (11-61)* | *9 : 6* |
| *AGRN - DOK7 clustering complex*** | *15* | *23.5 (10-71)* | *7 : 8* |
| *RAPSN* | *7* | *24 (1-71)* | *3 : 4* |
| *COLQ* | *5* | *22 (8-26)* | *0 : 5* |
| *Other**** | *8* | *26 (15-48)* | *5 : 3* |
| | *50* | *25.5 (1-71)* | *24 : 26* |

*Table 1. Baseline demographics.*
**Acetylcholine receptor deficiency (AChR def) included n=1 CHRND (delta), the remaining 14 had CHRNE (epsilon) genetic subtype. **Other included Slow-Channel CMS, Fast-Channel CMS, Glucosamine-Fructose-6-Phosphate Aminotransferase (GFPT1), Mutation in Agrin (AGRN), Sodium-dependent high-affinity choline transporter-1 (SLC5A7), Choline Acetyltransferase (CHAT) and Collagen-13 with Alpha-1-chain (COL13A1),*

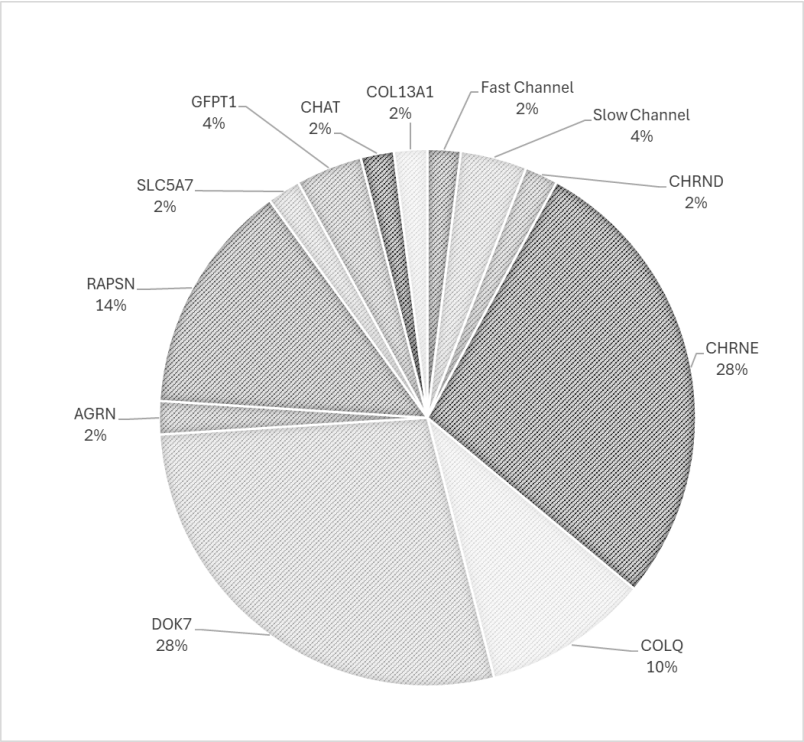



*Figure1. Relative proportions of different CMS genetic defects (n=49)*

**Outcome Measures:**

| QMG Item | *QMG normal range* | Total CMS cohort (n=49) | AChR def (n=15) | AGRN-DOK7clustering (n=15) | RASPN (n=7) | COLQ (n=5) |
|---|---|---|---|---|---|---|
| | | median (range) | median (range) | median (range) | median (range) | median (range) |
| Diplopia (seconds) | *0 - 60* | 60 (0-60) | 60 (0-60) | 60 (21-60) | 60 (0-60) | 60 (0-60) |
| Ptosis (seconds) | *0 - 60* | 12 (0-60) | 1 (0-60) | 7.5 (0-60) | 50 (0-60) | 12 (0-60) |
| Dysarthria (counting 1-50) | *1 - 50* | 50 (0-50) | 50 (35-50) | 50 (1-50) | 50 (33-50) | 50 (10-50) |
| Right Should Abd (secs) | *0 - 240* | 86 (0-240) | 174 (11-240) | 49 (0-240) | 142 (17-240) | 9 (1-38) |
| Left Shoulder Abd (secs) | *0 - 240* | 88.5 (0-240) | 200 (32-240) | 54.5 (0-240) | 150 (22-240) | 8.5 (1-113) |
| FVC (%) | *<50 to ≥80%* | 81 (0-125) | 86 (60-125) | 77 (45-110) | 82 (58-100) | 75 (26-93) |
| Right Hand Grip (kg) | *Male 0 to >45<br>Female 0 to >30* | 24 (0-46) | 21 (4-38) | 29 (8-46) | 32 (0-46) | 17.5 (9-35) |
| Left Hand Grip (kg) | *Male 0 to >35<br>Female 0 to >25* | 24 (0-51) | 19 (3-40) | 30 (8-51) | 30 (0-45) | 17 (9-33) |
| Head Lift (seconds) | *0 - 120* | 51 (0-120) | 97 (4-120) | 88 (0-120) | 72 (32-120) | 21.5 (0-43) |
| Right Hip Flex (secs) | *0 - 100* | 37.5 (0-100) | 45 (0-100) | 48 (0-100) | 49 (22-100) | 21.5 (12-42) |
| Left Hip Flex (secs) | *0 - 100* | 40 (0-100) | 39 (0-100) | 48 (0-100) | 42 (21-100) | 23 (14-63) |
| TOTAL QMG score | *0-39* | 12 (0-34) | 11 (2-22) | 13 (0-33) | 8 (4-14) | 18.5 (8-28) |
| STS1M | | 22 (0-45) | 19.5 (0-30) | 18 (0-45) | 25 (21-34) | 25 (18-37) |
| Distance walked 6MWT | | 445 (0-711) | 469 (100-698) | 364.5 (0-605) | 499 (277-711) | 432 (180-527) |
| MG-ADL | | 6 (0-21) | 6 (0-17) | 6 (0-21) | 5 (1-11) | 7 (2-16) |

**Adverse Events:** There were no adverse events associated with this study.

**Conclusions:** This first-of-a-kind study highlights the variability in fatigue and activity levels, along with patterns of muscle fatigue across the different CMS subtypes. This longitudinal cohort observation study provides an opportunity to explore the use of outcomes validated in myasthenia gravis in a CMS cohort. Further analysis of the results is pending to inform selection of relevant and reliable outcome measures for assessing and monitoring change in the CMS population within the UK.

**Trial registration:** This study was registered on 28 November 2022
**Keywords:** Congenital Myasthenic Syndromes, Natural History, Observational Study.

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