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CASE REPORT

Efficacy of ephedrine treatment in COLQ-related Congenital Myasthenic Syndrome (CMS): longitudinal quantitative assessment in a 71-year-old man

Giulio Gadaleta[1], Guido Urbano[1], Enrica Rolle[1], Ana Töpf[2], Liliana Vercelli[1]

[1] Neuromuscular Unit, Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy; [2] John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Introduction and aims. We describe a case of long-living COLQ-related congenital myasthenic syndrome (CMS) benefitting from ephedrine with an overall improvement quantified with functional measures.
Results. A 71-year-old man was referred with limb-girdle/axial myopathy and fatigability since infancy. In his thirties, a decremental response was observed at 3Hz-nerve stimulation, although testing seronegative for anti-neuromuscular junction antibodies. Later, whole exome sequencing (WES)identified a homozygous likely pathogenic variant in *COLQ*. After 6-month ephedrine treatment, the patient doubled the distance in the 6-minute-walk test and reached 10 metres in half of the time. His forced vital capacity (FVC) and first-second-forced expiratory volume (FEV1) increased, as well as all patient-reported outcomes. At the 12-month mark, the overall improvement remained consistent/further enhanced, except for a slight decrease in FVC.
Conclusions. This case confirms the efficacy of ephedrine treatment with global improvements in a COLQ-CMS in their late adulthood, demonstrated by quantitative outcome measures. Such indicators may be of interest in upcoming CMS therapeutical trials.

Keywords: congenital myasthenic syndrome, myasthenia, genetics, neuromuscular disorders, neurogenetics

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Correspondence
Giulio Gadaleta
E-mail: giulio.gadaleta@unito.it

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Background

Congenital myasthenic syndromes (CMSs) encompass a wide range of neuromuscular disorders frequently presenting with chronic weakness and fluctuating weakness. COLQ-related CMS is due to synaptic acetylcholinesterase (AChE) deficiency, often causing limb-girdle and axial weakness and early-onset respiratory insufficiency. Pyridostigmine administration has been reported as detrimental, while molecules with beta2-adrenoceptor agonist activity usually result in overall improvement [1,2].
We describe a case of infantile-onset myopathy with muscular fatigability, in which whole-exome sequencing (WES) revealed a homozygous likely pathogenic variant in the gene encoding the collagen-like tail subunit of asymmetric acetylcholinesterase (*COLQ*), with prominent quantitatively-assessed improvement after oral ephedrine treatment.

Case presentation

A 71-year-old man presented at the outpatient clinic for re-evaluation in a remarkable story of infantile-onset fatigability and dyspnea.

At first neurological examination in his thirties, he complained of long-term fluctuating weakness and easy fatigability from the age of 4 years, reporting generalized hypotonia at birth and insufficient head control during the first months of life. He denied any issues with motor delay but was never able to run longer distances due to early exhaustion. His brother died at the age of 3 months due to respiratory insufficiency, while his 4-year-old sister deceased after tonsillectomy under general anaesthesia. No consanguinity was reported in his family. He complained of dyspnea from adolescence, being present at rest and increasing with ordinary efforts. Cranial nerves were intact, except for the fatigability of tongue muscles against resistance; no slow pupillary light reflex was detected. A waddling gait with head ptosis and lumbar hyperlordosis was noted, together with difficulties in standing up from a chair and the floor. Muscles of both the upper and lower limb girdles were symmetrically involved as well as the finger, hand, and head extensor muscles with medical research council (MRC) scores between 3/5 and 3.5/5. Thigh and forearm muscles were bilaterally hypotrophic. Tendon reflex were reduced, while no bulbar or sensory deficits were detected.

Routine blood tests revealed a mild elevation of serum creatine kinase levels (225 IU/L, normal range: 30-190 IU/L).

Standard nerve conduction studies did not identify any significant abnormality. Electromyography revealed an increased number of polyphasic motor unit potentials (MUPs) characterized by low amplitude and early recruitment of new motor units under exertion at proximal limb muscles. Repetitive nerve stimulation (RNS) at a rate of 3Hz recording from the trapezius documented a significant decrement of compound muscle action potential (CMAP) amplitude accounting for almost 70% between the first and fourth motor response. No repetitive/double CMAP after single stimulus was registered. Nonetheless, a treatment trial with pyridostigmine caused subjective clinical worsening.

A muscle biopsy of the right femoral quadriceps muscle was performed at age 60, showing an unspecific "neurogenic" pattern, with modest fibre size variability, some angulated fibres, and some clusters of nuclei. Connective tissue was normally represented. After comprehensive histochemical, immunohistochemical and Western blot analyses, no specific enzyme or sarcolemmal protein defects were detected. Subsequently, a diagnosis of possible CMS was established, considering the negativity of anti-acetylcholine receptor (AChR) and anti-muscle-specific tyrosine kinase (MuSK) antibodies.

As part of the MYO-SEQ project [3], WES was conducted on the patient's DNA. The targeted analysis was focused on a set of 169 genes known to be associated with neuromuscular disorders, which identified a homozygous missense variant in the *COLQ* gene, specifically c.[1321A > G] (p.[Thr441Ala]), considered "likely pathogenic" based on ACMG guidelines [4].

At the age of 71 years the overall clinical picture only slowly progressed with the introduction of nocturnal non-invasive ventilation (NIV) due to hypoventilation from age 65, and motor, respiratory and patient-reported outcome measures (PROMs) were assessed. The patient showed a dropped head and easy fatigability in arm elevation, an interruption due to dyspnea at minute four of the 6-minute walk test (6MWT) was observed, (total distance achieved: 150 metres, 17.9% of healthy subject's predicted value based on gender, age, height of 178 cm and weight of 70 kg) [5] and a 10-metre walk test completed in 11 seconds (calculated gait speed of 0.91 m/s, 72.1% of predicted based on average walking speed per decade of age) [6]. At baseline, forced vital capacity (FVC) was 2.98L (78% of predicted) and forced expiratory volume in one second (FEV1) was 2.35L (81% of predicted). Myasthenia gravis activities of daily living (MG-ADL) scored 9/24 (talking:1; chewing:2; swallowing:1; breathing:2; impairment of ability to brush teeth of comb hair:1; impairment of ability to arise:2; double vision and eyelid droop:0); the short form-12 (SF-12) questionnaire resulted in physical component score (PCS) 35.3 and mental health component score (MCS) 28.41, both lower than mean values which have already been used as a reference in the neuromuscular field [7,8], and a total score of 21/47 pts (26%). The fatigue severity scale (FSS) yielded 57/63 pts, while the 9-item Rotterdam disability scale 29/36 pts.

A cardiac evaluation performed before starting a treatment with ephedrine ruled out potential contraindications. Progressively increasing doses of oral ephedrine were therefore prescribed, starting with 6.25 mg in the morning, to reach 25 mg b.i.d from day 40. No adverse symptoms or events were reported.

After 6 months of ephedrine, he reported significant improvement with absence of dyspnea at rest and only mild fatigue during daily life and submaximal efforts, although still on nocturnal NIV. Limb-girdle and head extension weakness was less evident, scoring between 3.5/5 and 4/5 on the MRC scale. He completed the 6MWT with a doubled distance of 337 metres (+ 124.7%, 40.1% of expected value for healthy patients) [5] and reached 10 metres in 6.19 seconds (1.62 m/s, + 78%, 128% of predicted for age) [6].

As for spirometry, his FVC was 3.54L (93% of predicted, +18.8%) and his FEV1 2.55L (89%, +8.5%).

A corresponding improvement in other functional tests and in all PROMs was also registered; in fact, MG-ADL scored 5/24 (chewing:1; swallowing:1; impairment of ability to brush teeth or comb hair:1; impairment of ability to arise from a chair:2; improvement of 16.7% of total score); SF-12: PCS 53.66, MCS 57.65, both better than reference values for neuromuscular cohorts, and a total score of 44/47(91%, +109.5%); FSS 21/63 (-36 pts, showing an improvement of 63.2% in fatigue severity score) and 9-item Rotterdam disability scale 36/36 pts (+7 pts, improvement of 24.1% in everyday autonomy).

After a 12-month treatment period with a consistent dosage, the patient experienced overall treatment benefits, except for a slight increase in fatigue in the neck extensors. Muscle strength was assessed and remained stable on MRC. In the 6MWT, the patient achieved a distance of 414 meters (+176% compared to the initial measurement and +22.8% from the 6-month value, equivalent to 49.3% of the expected value for healthy individuals) [5]. Furthermore, the patient completed a 10-meter walk in 7.6 seconds (equivalent to a speed of 1.32 m/s, which is 104% of the predicted value for age and represents a 45.1% improvement from the baseline measurement, albeit slightly slower than the values observed at the 6-month mark). Spirometry results indicated an FVC of 3.28L (87% of the predicted value, showing a 10.1% increase from the baseline measurement, but seemingly slightly worse than the 6-month value). The FEV1 remained stable at 2.35L (82% of predicted). The patient's functional ability, as assessed by the MG-ADL scale, remained unchanged (5/24). In terms of quality of life, the SF-12 assessment indicated a PCS score of 55.26 and an MCS score of 60.7, which

demonstrated even more positive values when compared to previous scores. The patient reported 13/63 points on the FSS questionnaire, indicating a further improvement in overall perceived fatigue (a 77.2% amelioration from baseline and a 38.1% from the 6-month mark). Additionally, the Rotterdam disability scale maintained a score of 36/36 points, confirming a good level of everyday autonomy.
As for safety, the patient did not report any significant adverse events, highlighting the long-term favorable profile of ephedrine even in older ages.

Conclusions

The presented case highlights the efficacy of a late ephedrine treatment on motor and respiratory function in a long-living COLQ-CMS patient, demonstrated by specific outcome measures, along with subjective reported outcomes.
Several types of CMSs, like DOK7-associated CMS, have shown treatability with beta2-adrenergic receptor agonists, demonstrating effectiveness in improving motor functions and overall outcomes in smaller study groups [9,10]. Furthermore, a recent meta-analysis examining the use of beta2-adrenergic agonists in COLQ-CMS confirmed positive effects in nearly all patients while cautioning against potential negative outcomes associated with the administration of AChE inhibitors [2]. Based on the cited literature, it is notable that most available studies are presented as small cohort reports, lacking randomized trials that consistently utilize defined outcome measures. Furthermore, the absence of specific drug dosage information, such as ephedrine, is a common occurrence.
In our case study, we underscored the main role of quantitative assessments in investigating treatment efficacy. Throughout a 12-month follow-up, these evaluations emerged as indicators of the necessity for dosage adjustments aligned with observed changes in functional scores. Moreover, these assessments substantiated the sustained efficacy of the treatment, even after decades from symptom onset, although confirming these findings will require more extensive monitoring and larger cohorts for validation.

Conflict of interest statement

The authors declare no conflict of interest.

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Author's contribution

G.G. and V.L. equally contributed to patient evaluation, data analysis and manuscript preparation; U.G. and R.E. participated in clinical data collection; T.A. performed and evaluated the genetic tests; L.V. supervised and completed the manuscript. The authors of this publication are members of the European Reference Network for rare neuromuscular diseases (EURO-NMD) – Project ID No. 739543.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical consideration

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
The present study was approved for publication in a scientific journal by the institutional ethical committee (Prot. n° 0016543, 8 February 2023). The local ethical committee also reviewed the written informed consent form (ICF) which was presented to the patient and collected for the same purpose and the photographic content acquisition. Informed consent for medical research was obtained and biological samples were submitted to the Newcastle Medical Research Council (MRC) Centre Biobank for Neuromuscular Diseases for which ethical approval was granted by the National Research Ethics Service (NRES) Committee North East–Newcastle & North Tyneside 1 (reference 19/NE/0028).

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