

# Electrical myotonia and antibiotic induced myasthenic crises: A novel CHRNE variant

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## Abstract

We describe a middle-aged lady who had developed childhood-onset chronic progressive external ophthalmoplegia, fatigable ptosis, and myopathic facies. Unique features of her clinical phenotype included facial weakness that failed to respond to treatment, exacerbation with antibiotic use and electrical myotonia. She responded well to 3,4-diaminopyridine. We highlight aspects of her presentation that led to clinical diagnosis – and, ultimately, genetic confirmation – of a congenital myasthenic syndrome. This underscores the importance of taking a family history and considering inherited causes in cases of seronegative myasthenia.

**Keywords:** Genetics, congenital myasthenia, seronegative myasthenia, ptosis, ophthalmoplegia

## CASE REPORT

A 54-year-old Indian lady presented to hospital with an acute cough, fever, dyspnea, dysphagia, and weakness. Shortly after receiving a dose of intravenous levofloxacin for pneumonia, she developed decompensated type 2 respiratory failure and was intubated.

She had developed partial ptosis and chronic progressive ophthalmoplegia since the age of three. In adolescence, she developed mild episodes of proximal weakness and dyspnea whenever she was given penicillins or macrolides for respiratory tract infections. In her late thirties, she was started on pyridostigmine by a neurologist after noting a decremental response on repetitive nerve stimulation.

Family history revealed consanguinity, with suspicion for an autosomal recessive disorder. The patient's parents were cousins and were unaffected. Her eldest brother had bilateral ophthalmoplegia from childhood and developed tremor-dominant Parkinsonism later. He was married to a first cousin – one of his three children, a daughter, had progressive ophthalmoplegia, myopathic facies with variable ptosis.

Examination revealed short stature, scoliosis, fatigable ptosis, complete bilateral ophthalmoplegia, with myopathic facies and bitemporal narrowing. Neck flexion, shoulder abduction, and hip flexion were weak. Reflexes were normal.

Serum electrolytes, lactate, creatine kinase, thyroid panel, acylcarnitines and contrasted MRI brain were normal. Repetitive nerve stimulation at 3Hz showed decremental response over abductor digiti minimi (59%) and nasalis (48%) and excluded a slow channel syndrome. On tibialis anterior and biceps electromyography, there was profound electrical myotonia with no myopathic changes. Anti-acetylcholine receptor and striated muscle antibodies were negative.

Pyridostigmine was increased to 90mg five times a day with empirical intravenous immunoglobulin (2g/kg) and intravenous hydrocortisone. Neck flexion and proximal weakness improved. She was treated with meropenem and was successfully extubated six days later.

Although this patient's presentation mimicked that of autoimmune myasthenia gravis, atypical features suggested an alternative diagnosis. The long duration of her symptoms, non-sustained response to pyridostigmine, seronegativity, positive family history and the lack of a typical waxing and waning course pointed towards congenital myasthenia.<sup>1</sup> Genetic studies were arranged.

Whole-exome sequencing identified a novel homozygous missense CHRNE gene variant (c.1267T>C, p.Cys423Arg), confirming diagnosis of a congenital myasthenic syndrome (CMS). This variant has not been reported in historical

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population databases until recent identification by our clinical geneticists.<sup>2</sup> CHRNE encodes the acetylcholine receptor (AChR) subunit, and variants at this codon have been reported to reduce functional AChR expression.<sup>3</sup>

She was started on 3,4-diaminopyridine. She reported mild paresthesias lasting 5 minutes after each dose. Her ptosis, bulbar and limb weakness improved. She remains ambulant with no myasthenic flares for the last two years. Interestingly, her ophthalmoplegia never improved with treatment – likely due to extraocular muscle atrophy from functional denervation.

## DISCUSSION

CMSs are diseases caused by inherited defects in neuromuscular transmission pathways. CMS patients can present with myasthenia that starts anytime between birth and adulthood. A genetic diagnosis is important to guide treatment, as pyridostigmine can be harmful in certain genetic forms of CMS (e.g. harmful variants in COLQ or DOK7).<sup>4</sup>

Clinical clues suggest that our patient's CHRNE variant acts by either reducing AChR expression or altering its kinetics. Our patient's features of early-onset ptosis with ophthalmoparesis, facial and bulbar weakness resemble CMS patients with AChR deficiency.<sup>5</sup> She does not have repetitive compound muscle action potentials, wrist or finger extensor weakness seen in autosomal dominant 'slow channel syndromes'.<sup>6</sup> A 'fast channel syndrome' remains a possibility, but it often presents with early onset hypotonia and abrupt respiratory crises<sup>7</sup> – microelectrode studies are required for diagnosis. The patient did not have limb-girdle weakness, stridor, contractures, episodic apnoea and pupillary abnormalities typical of variants in other CMS-related genes.<sup>8</sup> To investigate the pathogenic mechanism by which c.1267T>C affects neuromuscular transmission, future work should include in silico predictions, in vitro and muscle pathological studies of AChR expression and function. Ideally, segregation analysis should be performed, but the patient's family members declined this.

This patient's electrical myotonia was surprising, given absence of clinical myotonia. Her clinical features and intermittent exacerbations were not consistent with a myotonic dystrophy. SCN4A variants can cause both CMS and myotonia<sup>9</sup>, but myotonia has never been documented in CMS arising from AChR deficiency or, specifically, CHRNE variants. Autoimmune myasthenia gravis

was associated with myotonia in one case of anti-MuSK antibodies<sup>10</sup>, but it is rare for CMS to coexist with autoimmune myasthenia gravis, and our patient was seronegative. Myotonic-like waning discharges may be seen in radiculopathies and mononeuropathies, however myotonia was not restricted to a single muscle here, thus a focal process is unlikely to explain the patient's condition.

A second novel feature was the exacerbating role that drugs played in this patient's myasthenic crises. Unlike autoimmune myasthenia gravis, crises precipitated by drugs have not been reported with CHRNE variants. This patient's exacerbations were likely triggered by infection, however acute decompensation within hours of intravenous levofloxacin suggests antibiotic exposure was at least contributory. Macrolides are thought to suppress presynaptic acetylcholine release, while fluoroquinolones physically block postsynaptic AChR-gated ion channels.<sup>11–13</sup> In context of a CHRNE variant, it is conceivable that these antibiotic classes would also exacerbate congenital myasthenia where functional AChR expression is already reduced.

CHRNE-variant CMS commonly responds to pyridostigmine or 3,4-diaminopyridine.<sup>14</sup> However, response may be incomplete, or may wane after prolonged use. The effectiveness of salbutamol monotherapy as an alternative, first-choice treatment has been demonstrated in case series.<sup>15</sup> A meta-analysis of 208 CMS patients with CHRNE variants showed that beta-2 adrenergic receptor agonists were more effective than nine other classes of pharmacotherapy<sup>16</sup>, in the presence of primary AChR deficiency. Its effectiveness was independent of age of disease onset in the meta-analysis – reassuring us that it is never too late to initiate treatment for CMS. Unlike pyridostigmine, salbutamol can be used to treat COLQ- and DOK7-related CMS.<sup>17,18</sup>

In summary, we report a novel, biallelic missense CHRNE variant in a patient with childhood-onset chronic progressive ophthalmoplegia, myopathic facies, with exacerbations driven by infection and, possibly, drugs. We hope our patient's genetic diagnosis will guide treatment for her affected family members. We highlight the importance of taking a family history and having an index of suspicion for congenital causes, particularly in cases of seronegative myasthenia.

## DISCLOSURE

Consent: The patient gave written consent for the publication of this report.

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