Clinical and neurophysiological response to ephedrine in a patient affected with slow-channel congenital myasthenic syndrome

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Introduction. Slow-channel congenital myasthenic syndrome is an autosomal dominant inherited progressive neuromuscular disorder caused by abnormal gating of mutant acetylcholine receptors in the neuromuscular junction. Its pathological hallmark is selective degeneration of the endplate and postsynaptic membrane due to calcium overload. Pyridostigmine should be avoided in this syndrome, being quinidine or fluoxetine the current recommended therapies.

Case report. An 11-year-old girl with a limb-girdle phenotype of slow-channel congenital myasthenic syndrome presenting with a slowly progressive fatigable weakness at the age of 8 years. After a clinical worsening with pyridostigmine, empirically started before the exome sequencing results were available, a dramatic and sustained response to ephedrine monotherapy was observed. Whole exome sequencing revealed a de novo heterozygous mutation in *CHRNB1* gene: c.865G>A; p.Val289Met (NM_000747.2). An abnormal decrement in amplitude (23.9%) from the first to fifth intravollley waveform was revealed after repetitive peroneal nerve stimulation at low frequencies. In addition, a second smaller compound muscle action potential after the peak of the main M-wave in median, ulnar and peroneal motor nerves was observed.

Conclusion. Favorable responses to adrenergic agonists added to fluoxetine had been reported. However, to the best of our knowledge this is the first report on effective monotherapy with ephedrine in a slow-channel congenital myasthenic syndrome patient. Adrenergic agonists may be considered as a therapeutic option in patients with this syndrome.

Key words. Adrenergic agonists. *CHRNB1* gene. Congenital myasthenic syndrome. Ephedrine. Repetitive nerve stimulation. Slow-channel.

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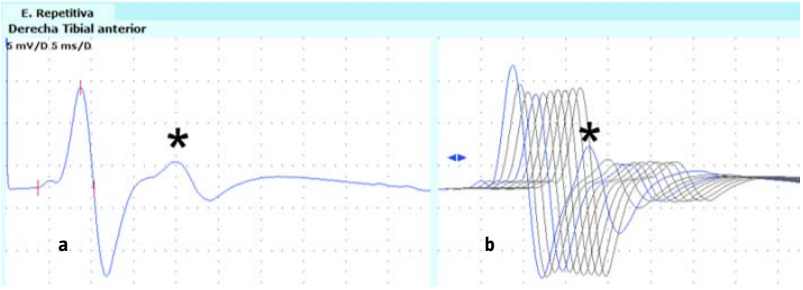
Introduction

Congenital myasthenic syndromes (CMS) comprise a heterogeneous group of genetic disorders, all of which impair signal transmission at the neuromuscular junction. The defects can affect presynaptic, synaptic or postsynaptic proteins. The clinical features and response to treatment vary according to the gene harboring the mutation(s) and the underlying molecular mechanisms that impairs signal transmission [1]. Slow-channel congenital myasthenic syndrome (SCCMS) is a postsynaptic disorder that may present at any age and is mainly characterized by progressive fatigable muscle weakness. Dominant gain-of-function mutations result in a kinetic impairment of the acetylcholine receptor (AChR), which gives rise to an abnormally prolonged channel opening. Sustained AChR activation causes prolonged synaptic currents that result in a depolarization block. This is associated with calcium overload, which ultimately may lead to an endplate myopathy, secondary to the degeneration of the endplate and postsynaptic membrane [2].

The use of pyridostigmine and other agents designed to increase AChR activation (e.g, 3,4-DAP) is not recommended in SCCMS. On the other hand, patients may benefit from long-lived open-channel blockers of the receptor, such as quinidine or fluoxetine, which appear to block open AChR channels and minimize the clinical effects of prolonged AChR opening [1-3]. Despite its proven efficacy, significant adverse effects have been observed in some patients treated with fluoxetine. β2-adrenergic agonists, such as ephedrine and salbutamol, have proven to be effective not only in autoimmune myasthenia but also in some CMS, including *DOK7, COLQ* and *AGRN*-related CMS [1,2,4]. Moreover, addition of β_2-adrenergic agonists to acetylcholinesterase inhibitors has reported to be beneficial in patients with AChR deficiency, fast channel syndrome, *CHAT*-related CMS, and CMS secondary to glycosylation defects. Adrenergic agonists seem to enhance neuromuscular junction synaptic structure by counteracting the detrimental effects of long-term acetylcholinesterase inhibitors on the postsynaptic neuromuscular junction [1,2]. To our

Figure. a) Peroneal motor waveforms, stimulating below fibular head and recording the tibialis anterior muscle: a single supramaximal stimuli elicite a second smaller CMAP 7,5 ms after the peak of the main M-wave (*); b) 3 Hz repetitive nerve stimulation in the same nerve results in a 23.9% CMAP amplitude decrement at rest. Note that the decremental response is present in both waves: M-wave and the second CMAP (*).



knowledge, however, significant beneficial responses to ephedrine monotherapy in SCCMS have not been reported so far.

Here, we report the case of a Spanish girl with a SCCMS, who showed a dramatic and sustained beneficial response to ephedrine monotherapy.

Case report

This 11-year-old girl with SCCMS was the first child of a healthy and nonconsanguineous couple. She was born at term by eutocic delivery after a normal pregnancy. Her achievement of motor milestones was normal and she was physically and cognitively normal, with only mild clumsiness in gross and fine motor skills. She started presenting a slowly progressive fatigable weakness at the age of 8, with difficulties in climbing stairs and walking long distances. At first, these symptoms were referred to be episodic, with variable periods of time in which she felt well. Over time, both weakness and fatigability worsened. When she was assessed in our center, at the age of 10 years and 5 months, she was unable to climb stairs, run or walk more than a short distance. Moreover, she was not able to rise unassisted from the floor without 'climbing up the body' (Gowers sign). Bulbar or respiratory symptoms were not present. On examination, hyperlordosis, a proximal limb weakness (MRC: 4–/5) with slight wadding gait was evident, without ptosis, ophthalmoplegia, facial weakness or distal involvement. Forearm extensor and cervical muscles were not found to be weak. All the complementary tests, including hemogram, metabolic screen, creatine kinase, thyroid function, exercise-induced ischemic test, electrocardiogram, ocular exam, cerebral and spinal magnetic resonance imaging, electromyography (EMG) –without repetitive stimulation–, were normal. Whole exome sequencing (WES) was requested.

A CMS presenting with a limb-girdle phenotype was suspected, therefore a new EMG with repetitive stimulation (RNS) was required. An abnormal decrement in amplitude (23.9%) from the first to fifth intravollley waveform was revealed after repetitive peroneal nerve stimulation at low frequencies (3 Hz) (Figure). In addition, a second smaller CMAP after the peak of the main M-wave in median, ulnar and peroneal motor nerves was observed. Since the genetic diagnosis was still unavailable, we empirically tried a single 30 mg dose of pyridogstigmine. A significant improvement was observed 45 minutes after administration; therefore, we decide to start pyridostigmine treatment at 15 mg every 8 hours. Surprisingly, a clinical worsening, characterized by an increase in muscle weakness, was observed in the following 48 hours after pyridostigmine onset and it was, subsequently, withdrawn. Given this response, we decided to start treatment with ephedrine (25 mg/8 h). At that stage, we acknowledged that some types of CMS might worsen with pyridostigmine (i.e., *DOK7*-CMS, *COLQ*-CMS and SCCMS) and regarded *DOK7*-CMS as most plausible due to the limb-girdle phenotype. An outstanding beneficial response, sustained now for 18 months, was observed upon ephedrine treatment. The motor functional ability of the patient has significantly improved, recovering the ability of climb stairs, walk large distances and even run. On clinical examination, strength in proximal upper limbs has increased from 4–/5 to 5/5. According the Gower's sign severity scale proposed by Chang et al [5], the improvement in muscle strength allowed the patient to go from a score of 7 (prone crawl position, both hands on thigh) to a score of 0 (normal).

Eleven months after the ephedrine therapy was started, no decrement was detected with RNS in peroneal, median and tibial nerves. However, a second CMAP was still present on the aforementioned nerves.

WES was used to identify disease associated variants. The analysis revealed a heterozygous mutation in *CHRNB1* gene (acetylcholine receptor): c.865G>A; p.Val289Met (NM_000747.2). No described allele frequencies have been found for this variant in ExAC, 1000g or gnomAD databases. This variant was already reported and functionally characterized in 1996 [2] and had been associated with SCCMS. 'In

silico' predictors such us SIFT, polyphen, Mutation Taster and CADD_Phred score confirm the pathogenicity of this variant. Sanger Sequencing revealed that the variant found was no present in the parents, which confirmed that it was 'de novo'.

Discussion

To date, at least 15 different mutations underlying the SCCMS have been identified [2]. c.865G>A; p.Val289Met mutation occurs in the M2 domain and has been previously associated with variable phenotypic expression [2,6]. Mutations at this region are thought to line the channel pore and act predominantly by slowing channel closure, thus resulting in long individual channel openings [2].

The clinical phenotype of SCCMS is variable, and both early severe early or late moderate onsets may occur [2]. Most cases present severe weakness of the cervical, scapular, wrist, and finger extensor muscles [2]. Ptosis, ophthalmoparesis, dysarthria, dysphagia, proximal limb weakness, and respiratory insufficiency may also occur [2,7]. Despite its variability, SCCMS is not included among CMS subtypes with typical limb-girdle muscular dystrophy (LGMD)-like phenotype [8], and clinicians might probably rather consider SCCMS in the presence of other clinical clues, such as the selective involvement of the neck and dorsal forearm muscles [2]. In the case we report, the clinical picture was quite different, with a childhood onset characterized by progressive proximal fatigable weakness. The initial suspicion pointed to *DOK7*-CMS, one of the CMS that typically present a LGMD-like phenotype, especially after a worsening with acetylcholinesterase inhibitors was observed. Regarding the improvement following the first dose of pyridostigmine, such transient response was also described in anecdotical cases [9], thus leading to an erroneous feeling of effectiveness.

Ephedrine is an alkaloid from the group of phenyl-ethyl-amines, originating from the plant ephedra. Due to its sympathomimetic properties, it is used for asthma, as a decongestant, and in ophthalmology as a supplement of atropine. It has been reported effective in *COLQ*-, *LAMB*2-, *DOK7*-, and *AGRN*-related CMS [1,2]. We are not aware of any SCCMS reported case treated with ephedrine or salbutamol monotherapy, but some experimental data is available. In transgenic mouse model of SCCMS (εL221F mutation), ephedrine-treated mices only showed a modest benefit of the treatment with these β_2-adrenergic receptor agonists [9]. In a clinical scenario, there are some references to favorable responses of β_2-adrenergic receptor agonists in combination with fluoxetine [1,4,10] but none reported its use in monotherapy.

The response observed in our patient cannot be directly extrapolated to other SCCMS patients and we realize that there may be differences depending on pathophysiological mechanisms related to the type of mutation, since these can affect agonist binding, the transduction of the signal from agonist binding to channel opening, and the actual opening and closing of the channel gate. Hence, it is plausible that some cases may respond well to fluoxetine while others may respond to ephedrine or a combination of both.

A deeper knowledge of the pathophysiological implications of different mutations is required to improve therapeutic individualization. Although more evidence is needed to support the use of ephedrine in SCCMs cases, our observation argues in favor its consideration as a potentially useful therapy, offering to some patients an alternative treatment option to fluoxetine or quinidine.

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Respuesta clínica y neurofisiológica a la efedrina en un paciente con síndrome miasténico congénito de canal lento

Introducción. El síndrome miasténico congénito de canal lento, o síndrome de canales lentos, es un trastorno neuromuscular progresivo hereditario, autosómico dominante, causado por una activación anormal de los receptores de la acetilcolina en la unión neuromuscular. La alteración histopatológica característica es la degeneración selectiva de la placa terminal y la membrana postsináptica debido a la sobrecarga de calcio. La piridostigmina debe evitarse en este síndrome, y la quinidina o la fluoxetina son las terapias recomendadas actualmente.

Caso clínico. Niña de 11 años con un fenotipo de cinturas de síndrome miasténico congénito de canal lento que presenta debilidad y fatiga lentamente progresivas desde los 8 años. Tras un empeoramiento clínico con piridostigmina, iniciado empíricamente antes de que los resultados de la secuenciación del exoma estuvieran disponibles, se observó una respuesta espectacular y sostenida con efedrina en monoterapia. La secuenciación del exoma reveló una mutación heterocigota *de novo* en el gen *CHRNB1:* c.865G>A; p.Val289Met (NM_000747.2). El estudio electromiográfico con estimulación repetitiva en el nervio peroneo mostró una disminución anormal en la amplitud (23,9%) y también la génesis de un segundo potencial de acción muscular compuesto más pequeño después del pico de la onda M principal en los nervios motores mediano, cubital y peroneo.

Conclusión. Aunque se han documentado respuestas favorables a agonistas adrenérgicos en asociación con la fluoxetina, ésta representa la primera aportación que documenta una respuesta clínica relevante con efedrina en monoterapia en un paciente con síndrome miasténico congénito de canal lento. Los agonistas adrenérgicos pueden considerarse una opción terapéutica en pacientes con este síndrome.

Palabras clave. Agonistas adrenérgicos. Canal lento. Efedrina. Estimulación nerviosa repetitiva. Gen *CHRNB1.* Síndrome miasténico congénito.