Case Report

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Effective treatment with oral Salbutamol on late onset respiratory impairment in a DOK7 Congenital Myasthenia Syndrome: a case report

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ABSTRACT

Introduction: DOK7 gene deficiency is a neuromuscular disease with an alteration in post-synaptic neuromuscular junction, leading to progressive respiratory impairment. Although, the therapy is not standardized, adrenergic agonists are suggested as first-line treatment.

Case presentation: Our patient had an ambiguous late childhood-onset and had a generalized muscle weakness free of respiratory symptoms during the early phase of the disease. Subsequently, when the respiratory muscle and the diaphragm involvement was impaired, a substantial loss of respiratory function with hypopneas and severe desaturation was detected. It was noteworthy the striking respiratory beneficial impact of oral salbutamol in the resolution of symptoms and functional impairments, leading to a remarkable respiratory improvement and a better quality of life.

Conclusion: Oral salbutamol treatment combined to a timely clinical recognition led to an outstanding respiratory improvement

Key words: Congenital Myasthenia Syndrome, *f*dl, myopathy, DOK7, respiratory insufficiency

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Introduction

Congenital myasthenic syndromes (CMSs) are a genotypically and phenotypically heterogeneous group of neuromuscular disorders, which have in common an impaired neuromuscular transmission. Specifically, CMS in DOK7 gene deficiency is a neuromuscular disease with an alteration in post-synaptic neuromuscular junction. The typical disease onset is in the second year of life, displaying ptosis, limb-girdle weakness, frequent falls or gait waddling and progressive respiratory dysfunction [1]. Actually, the therapy prescribed is oral salbutamol, which has been associated to an improvement of DOK7 CMS [2]. We describe a tricky case of CMS with an adulthood-onset respiratory impairment, which is a rare condition, completely solved by oral salbutamol administration.

Case presentation

In 2018, a 22-year-old man referred to our pulmonary clinic for evaluation of recent onset of dyspnea on exertion, night loud snoring, sudden arousal during sleep, morning headache, daytime sleepiness. He reported, also, a late childhood-onset (around seven years old) of remarkable history of fatigue, muscle contractures, fasciculations, general weakness and difficulty in climbing stairs with a diagnosis of unspecific dystrophy, never investigated. The symptoms were not fluctuating. He never had the ability to run. During the visit the general examination showed bilateral ptosis without ophthalmoplegia or dysmorphic characteristics, nasal speech, dysphonia, upper and lower limb-girdle muscular weakness, diffuse hypotonia and hypotrophy. Body Mass Index (BMI) was normal 21,0 kg/m². On the other hand, Epworth sleepiness scale (ESS): 11/24 and STOP-Bang Questionnaire: 4/8 underlined a high risk for sleep apnoea. Blood tests were normal except for Creatine phosphokinasi (CPK) 474 U/L, Mioglobine 80.440 μg/L. The pulmonary function tests (PFTs) measured Total Lung Capacity (TLC) 84%, Forced Vital Capacity (FVC) 73% and no significant volume reduction in lying 30° position was recorded. Diffusing Capacity of Carbon Monoxide (DL_{CO}) 86% and the Krogh factor 121% were normal. On the contrary, the maximal inspiratory (MIP) and expiratory pressure (MEP) were remarkable lower, respectively 60 cmH_2O e 53 cmH_2O. The blood gas analysis, performed in room air, highlighted a compensated metabolic alkalosis with normoxaemia. Overnight home respiratory polygraphy showed a hypoventilation pattern with severe desaturation. The cardiopulmonary exercise test assessed a reduced exercise tolerance with muscle exhaustion at workloads reduced than predicted, although normal ventilatory efficiency and lactate threshold within age limits. Finally, the diaphragmatic ultrasound, performed with a convex probe in lying 30° position, assessed a reduced excursion (2 cm). After the clinical evaluation he was labeled as myopathy, non-invasive ventilation (NIV) was prescribed and settled, in order to improve his nocturnal respiratory pattern and a neurological consultation was required. In the meantime, muscle biopsy revealed nonspecific myopathic changes and the neurologist started a pharmacological therapy with Pyridostigmine 30 mg three times daily. By this time, oral Pyridostigmine was administered for six months and, during our second evaluation, was reported worsening of all systemic and respiratory symptoms. The patients presented frequent falls, gait difficulties, impossibility in daily activities and a critical respiratory deterioration. Meanwhile, the genetic sequencing revealed a Congenital Myasthenia Syndrome (CMS) with DOK7 (downstream of tyrosine kinase 7) gene mutation. With this scenario, the multidisciplinary team (pulmonologist, neurologist and pharmacologist) decided to stop Pyridostigmine, in line with literature, and start a therapy with oral salbutamol 4 mg three times daily as add-on therapy with NIV. Oral salbutamol administered for at least one-month improved all symptoms. At six months of administration get better muscle weakness, daytime sleepiness, snoring, headache and dyspnea on exertion without remarkable adverse effects. The blood gas analysis showed a normal acid-basic balance with normoxaemia. Moreover, respiratory muscle strength tests were normalized, respectively MIP 90 cmH_2O and MEP 91 cmH_2O. No more nocturnal hypoventilation pattern was seen at overnight respiratory polygraphy and, finally, the cardiopulmonary exercise test showed normal oxygen cost of work ($\Delta V'O2/\Delta power$: 11.06 ml/min/W), with linear growth pattern.

Discussion

Congenital Myasthenia Syndromes (CMSs) [1, 3, 4, 9, 11] includes a group of rare neuromuscular inherited disorders, genotypically and phenotypically heterogeneous, resulting in altered encoding for presynaptic, synaptic, and postsynaptic proteins with impaired neuromuscular junction signal transmission. Due to genetic heterogeneity alterations, the therapy is not standardized, but includes cholinergic agonists (pyridostigmine and 3,4-diaminopyridine), adrenergic agonists (salbutamol/albuterol and ephedrine) and long-lived open-channel blockers of acetylcholine receptor ion channel (fluoxetine and quinidine). A genetic diagnosis is highly recommended before starting a pharmacologic treatment, because a medication could be beneficial in one syndrome and detrimental in another genetic mutation. In fact, if anticholinesterase therapy is effective in most syndromes, it is contraindicated in endplate (EP) acetylcholinesterase (AChE) deficiency, the slow-channel syndrome, DOK7 myasthenia, and β2-laminin deficiency, that respond favorably to salbutamol, a selective β2-adrenergic agonist [2,9]. Although, the precise mechanism of action of β2-adrenergic agonists at the neuromuscular junction (NMJ) is not fully understood, their effect on the postsynaptic stabilisation of the membrane of the NMJ was demonstrated on mice models with DOK7 CMS, showing an improved both neurotransmission and structural integrity of the NMJ and therefore an increased number of active NMJs after administration of salbutamol [9,10]. An increase in the number of detectable NMJs following treatment suggests there is enhanced stability of the synaptic structure [9, 10].

Specifically, our patient was diagnosed with CMS DOK7 gene mutation [5,6], which is involved in normal development and maintenance of the neuromuscular junction [1,7] and clinically deteriorate with cholinesterase inhibitors (Figure 1). In particular, our patient had an ambiguous late childhood-onset and had a generalized muscle weakness free of respiratory symptoms during the early phase of the disease. Subsequently, when the respiratory muscle and the diaphragm involvement was impaired, a substantial loss of respiratory function was detected. The respiratory muscle strength dysfunction was accompanied by significant hypopneas with severe desaturation, revealed during sleep study. Treatment of this patient was started, firstly, with a Pyridostigmine, with no improvement and even a worsening trend. After the genetic diagnosis was made, it was switched to oral salbutamol [8], resulting in a striking clinical and functional improvement. The combination therapy NIV and oral salbutamol achieved an early success since the first month of administration. In particularly, the respiratory muscle strength tests, MIP and MEP, which

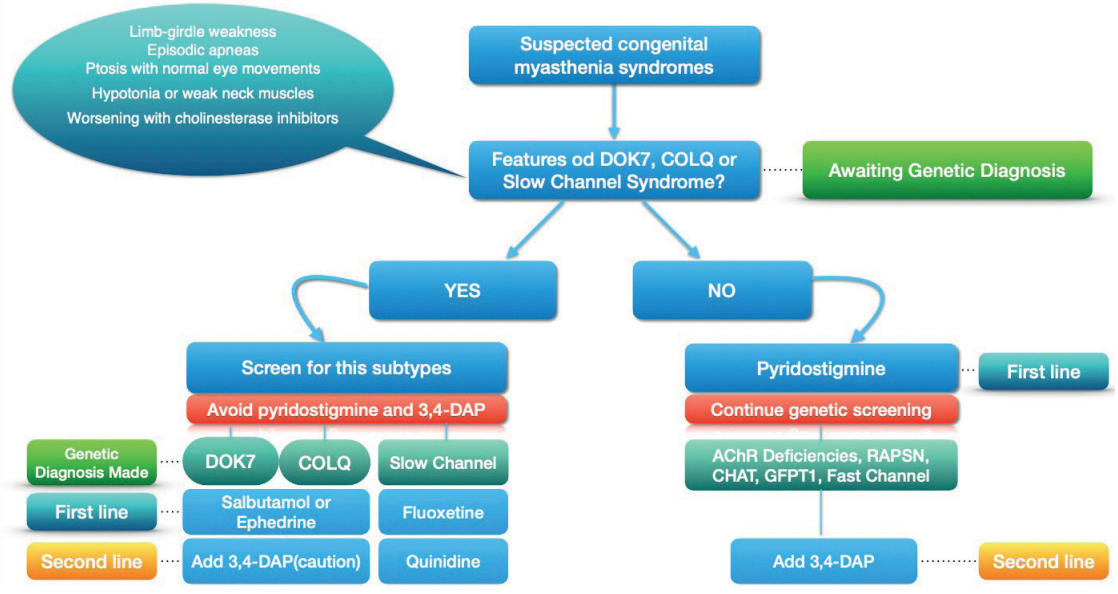

Figure 1. A systematic clinical approach and treatment strategies in different types of congenital myasthenia syndromes.

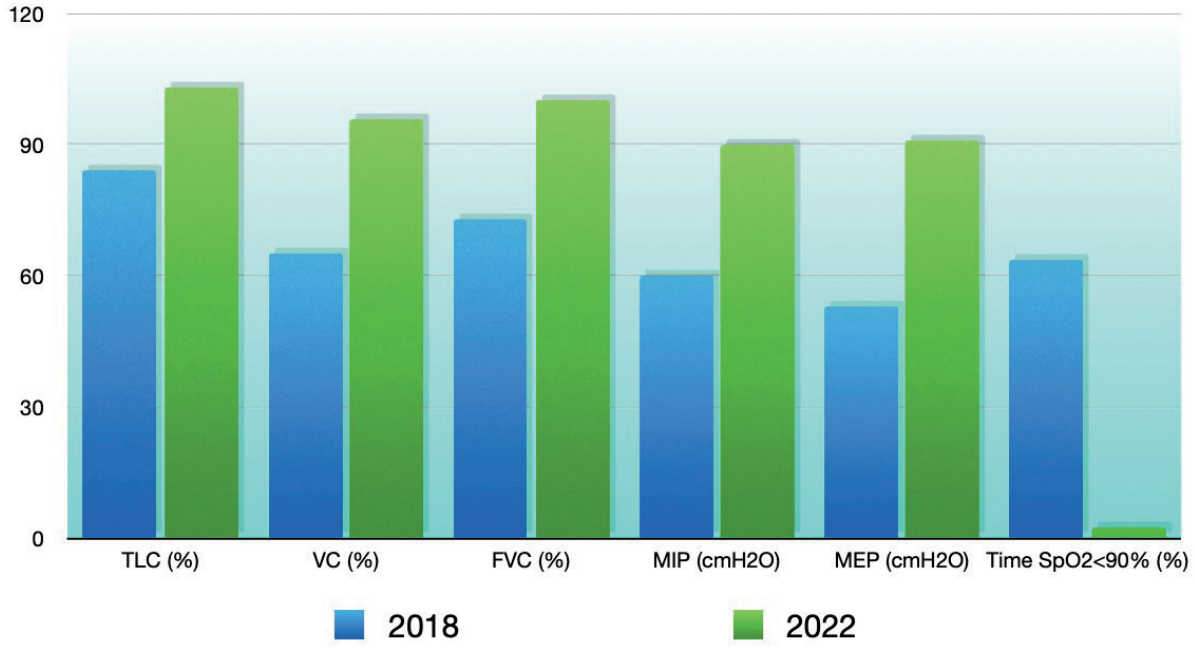

Figure 2. Comparison of the pulmonary function changes before the precise diagnosis (2018) and after constant treatment with oral salbutamol (2022).

allow a simple assessment of global respiratory muscle strength, were significantly improved demonstrating the promptly therapeutic efficacy of salbutamol. Furthermore, although the spirometric values were within normal range at baseline, we noticed a significant boost in the respiratory function testing.

At six months of follow up, pulmonary function tests (PFTs), respiratory muscle strength tests and sleep study assessed the respiratory improvement, as shown in Figure 2. After that, also the cardiopulmonary study confirmed the remarkable respiratory beneficial impact of oral salbutamol in the resolution of symptoms and functional impairments.

Conclusion

In conclusion:

- genetic diagnosis is highly recommended before starting a pharmacologic treatment, because a medication could be beneficial in one syndrome and detrimental in another;
- oral salbutamol treatment combined to a timely clinical recognition led to an outstanding respiratory improvement and a better quality of life.

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Abbreviations

BMI: Body Mass Index
CMS: Congenital myasthenic syndrome
CPK: Creatine phosphokinasi
DL_{CO}: Diffusing Capacity of Carbon Monoxide
ESS: Epworth sleepiness scale
FVC: Forced Vital Capacity
MEP: Maximal Expiratory Pressure
MIP: Maximal Inspiratory Pressure
MuSK: Muscle-Specific tyrosine Kinase
NIV: Non-invasive ventilation
NMJ: Neuromuscular junction
PFTs: Pulmonary Function Tests
TLC: Total Lung Capacity

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