

Congenital myasthenic syndrome due to mutation in *CHRNE* gene

Wrodzony zespół miasteniczny spowodowany mutacją w genie *CHRNE*

Aleksandra Jastrzębska¹, Anna Potulska-Chromik¹, Anna Kostera-Pruszczyk¹

¹ Department of Neurology, Medical University of Warsaw, Warsaw, Poland

DOI:10.20966/chn.2017.52.401

STRESZCZENIE

Wrodzone zespoły miasteniczne (CMS) należą do grupy chorób rzadkich, heterogennych genetycznie. Są zaliczane do chorób złącza nerwowo – mięśniowego. Wśród CMS najczęściej występują postsynaptyczne CMS. Objawy mogą być zbliżone do objawów autoimmunologicznej miastenii, a diagnostyka opiera się na badaniach genetycznych. W naszej pracy prezentujemy przypadek chłopca z wrodzonym zespołem miastenicznym spowodowanym mutacją w genie *CHRNE* i z dodatnim wywiadem rodzinnym w kierunku autoimmunologicznej miastenii.

Słowa kluczowe: Wrodzone zespoły miasteniczne, mutacja *CHRNE*, miastenia gravis

ABSTRACT

Congenital myasthenic syndromes (CMS) belong to a group of rare genetically heterogeneous diseases that affect neuromuscular junction. The most frequent are postsynaptic CMS. Symptoms may mimic myasthenia gravis and diagnosis relies on genetic testing. We report a case of a boy with CMS due to *CHRNE* mutation and positive family history of autoimmune myasthenia gravis.

Key words: Congenital myasthenic syndromes, *CHRNE* mutation, myasthenia gravis

INTRODUCTION

Childhood neuromuscular junction disorders (NMJ) include both autoimmune myasthenia gravis (MG) and congenital myasthenic syndromes (CMS) [1]. CMS constitute a heterogeneous group of rare genetic diseases [2]. They are caused by mutations of a number of genes encoding proteins present at presynaptic, synaptic or postsynaptic part of NMJ. Postsynaptic forms are most frequent and account for approximately 75–80% of CMS patients [3]. Although there is very little data about the epidemiology of congenital myasthenic syndromes, in the UK prevalence of genetically confirmed congenital myasthenia is 9.2 per million children [1]. Positive family history does not always exclude diagnosis of autoimmune myasthenia gravis (MG), as familial MG accounts for approximately 2–3% of MG cohorts. Therefore, proper identification of CMS patients is vital for the choice of optimal treatment.

We report a case of a boy with a positive family history of NMJ disease and discuss the diagnostic and therapeutic options.

CASE REPORT

The boy was first seen at our outpatient Clinic with persistent symmetric ptosis at the age of 11.5 months. He was born at term after uncomplicated pregnancy. When he was 3–4 months old the parents noticed symmetrical ptosis with fluctuating severity, prominent within an hour after awakening. There were no swallowing or suckling dysfunction, no strabismus, or dyspnea. Due to history of recurrent bronchitis and gastroesophageal reflux disease, cystic fibrosis was excluded by his pediatrician. Cardiac ultrasound revealed patent foramen ovale (PFO), his Holter-ECG

monitor was not relevant. Developmental milestones were normal, he started walking unsupported at 14 months of age. His parents were not related. He had a healthy older brother. Family history was not relevant for NMJ disease. Preliminary diagnosis of CMS was made. Repetitive nerve stimulation (RNS) test performed at that time was within normal limits, AChRab were negative. Molecular testing for CMS was not available at that time.

He was seen by us again when he was 3 yo. There was marked ptosis and mild weakness and fatigability of proximal lower extremity muscles and nasal speech.

RNS was repeated and revealed NMJ abnormalities. It was performed from radial nerve, the amplitude of first response was normal (4.6 mV). Decrement was 35%. There was no facilitation. Double CMAP was not recorded. The boy was started on β_2 agonist – salbutamol – which was not effective. Then pyridostigmine was introduced with a good clinical result. AChRab were negative on several retests.

A year later seropositive MG was diagnosed in his paternal grandfather raising possibility of familial autoimmune MG in the boy. He started treatment with prednisone without clear improvement.

Genetic testing was completed confirming compound heterozygous *CHRNE* mutation – c.803–2A>G which was previously reported as causative of CMS [4] and c.965G>A (p.Cys322Tyr) which until now has not been described in the specific databases. Both his parents are carriers of heterogeneous *CHRNE* mutation which confirms that mutations were inherited by the boy as autosomal recessive trait (OMIM # 100725).

At last follow-up, he had severe limitation of eye movements, minimal weakness of facial muscles and no limb

muscle weakness on a stable daily dose of pyridostigmine 3x60 mg. He is physically active.

DISCUSSION

Our case illustrates clinical difficulties in diagnosing congenital myasthenic syndrome in a patient with family history of autoimmune MG. Autoimmune MG is rare and found usually in siblings or cousins [5]. However, several families with MG in subsequent generation were described [6]. Families with seropositive and seronegative MG patients were reported as well [7].

AChR is a pentameric complex composed of four subunits – *CHRNA1*, *CHRNBI*, *CHRND* and *CHRNE*. Most of the mutations occur in *CHRNE* and produce an AChR deficiency syndrome [8]. Patients with mutations of the AChR epsilon subunit (*CHRNE*) usually have symptoms at birth or in the first years of life. Ptosis is a presenting feature in most of them followed by limitation of eye movement [9]. Autoimmune MG only exceptionally starts as early as the first year of life, although seronegativity is relatively frequent in young MG patients [10, 11].

Coexistence of autoimmune seropositive MG with CMS was described in patients with CMS caused by *CHRNE* mutations suggesting that such mutations can predispose to the development of AChR-positive MG [12, 13]. Also *CHRNA1* locus was implied as a minor susceptibility gene for developing MG [14]. We did not have an opportunity to verify *CHRNE* mutation status in a boy's grandfather who developed late-onset autoimmune MG. It is extremely uncommon for CMS and MG to associate in the same subject [13], but co-occurrence of NMJ of different etiology in a single family is even less likely. This is why we undertook a trial of immunosuppression in the boy, but the response to glucocorticoids was poor, further confirming the genetic nature of his disease. Symptomatic treatment with pyridostigmine alone improved strength of the patient significantly, as reported in other CMS as well [15]. Diagnosis of NMJ can be challenging in a family with both MG and CMS.

REFERENCES LITERATURE

- [1] Parr J.R., Andrew M.J., Finnis M., et al.: Jayawant, How common is childhood myasthenia? The UK incidence and prevalence of autoimmune and congenital myasthenia. *Arch Dis Child* 2014; 99: 539–542.
- [2] Engel A.G., Shen X.M., Selcen D., et al.: Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. *The Lancet. Neurology* 2015; 14: 420–434.
- [3] Lorenzoni P.J., Scola R.H., Kay C.S., et al.: Congenital myasthenic syndrome: a brief review. *Pediatric neurology* 2012; 46: 141–148.
- [4] Beeson D., den Dunnen J.: Cholinergic receptor, nicotinic, epsilon (*CHRNE*). *Leiden Muscular Dystrophy pages*. Address: <http://www.dmd.nl/>, (accessed 26–06–2017.).
- [5] Landouze G., Knight M.A., Stanescu H., et al.: A candidate gene for autoimmune myasthenia gravis. *Neurology* 2012; 79: 342–347.
- [6] Pirskanen R.: Genetic aspects in myasthenia gravis. A family study of 264 Finnish patients. *Acta Neurol Scand* 1977; 56 (5): 365–388.
- [7] Provenzano C., Arancio O., Evoli A., et al.: Familial autoimmune myasthenia gravis with different pathogenetic antibodies. *J Neurol Neurosurg Psychiatry* 1988; 51 (9): 1228–1230.
- [8] Rodriguez Cruz P.M., Palace J., Beeson D.: Inherited disorders of the neuromuscular junction: an update. *Journal of neurology* 2014; 261 (11): 2234–2243.
- [9] Burke G., Cossins J., Maxwell S., et al.: Distinct phenotypes of congenital acetylcholine receptor deficiency. *Neuromuscular disorders* : NMD 2004; 14 (6): 356–364.
- [10] Ashraf V.V., Taly A.B., Veerendrakumar M., et al.: Myasthenia gravis in children: a longitudinal study. *Acta Neurol Scand* 2006; 114 (2): 119–123.
- [11] Evoli A., Batocchi A.P., Bartocioni E., et al.: Juvenile myasthenia gravis with prepubertal onset. *Neuromuscular disorders* : NMD 1998; 8 (8): 561–567.
- [12] Santos E., Moreira I., Coutinho E., et al.: Congenital myasthenic syndrome due to mutation in *CHRNE* gene with clinical worsening and thymic hyperplasia attributed to association with autoimmune-myasthenia gravis. *Neuromuscular disorders*: NMD 2015; 25 (12): 928–931.
- [13] Croxson R., Vincent A., Newsom-Davis J., et al.: Myasthenia gravis in a woman with congenital AChR deficiency due to epsilon-subunit mutations. *Neurology* 2002; 58: 1563–1565.
- [14] Heckmann J.M., Morrison K.E., Emeryk-Szajewska B., et al.: Human muscle acetylcholine receptor alpha-subunit gene (*CHRNA1*) association with autoimmune myasthenia gravis in black, mixed-ancestry and Caucasian subjects. *J Autoimmun* 1996; 9: 175–180.
- [15] Das A.S., Agamanolis D.P., Cohen B.H.: Use of next-generation sequencing as a diagnostic tool for congenital myasthenic syndrome. *Pediatric neurology* 2014; 51: 717–720.

Correspondence:

Anna Kostera-Pruszczyk, Klinika Neurologii WUM, ul. Banacha 1a, 02-097 Warszawa, akostera@wum.edu.pl