Hypotonia in newborns and infants is a common neurological sign that may reflect underlying systemic illnesses or dysfunction of the nervous system. Depending on the localization the latter can be classified in two groups: supraspinal disorders (including the brain, brainstem and cervical spinal junction) that we can call central hypotonia and segmental conditions (affecting the anterior horn cell, the peripheral nerve, neuromuscular junction or the muscle) which are called motor unit hypotonia. The differential diagnosis may cause challenge for the clinicians and it often requires complex procedures. The history, the general physical and neurological examinations are able to narrow down the possible diagnoses considerably.

Preterm delivery, connatal infections, malnutrition, cardiovascular abnormalities, metabolic and endocrine disorders, drug poisoning are the main causes of systemic origin of hypotonia.

The significant cause of central hypotonia is the presence of brain injury (hypoxic and/or hemorrhagic brain lesions), chromosomal abnormalities or brain malformations.

Myasthenia is an illness of the motor unit caused by dysfunction of the neuromuscular signal transmission, which is characterized by weakness and fatigability of the muscles. From the etiological point of view two different groups of the neonatal myasthenia can be distinguished: congenital myasthenic syndromes and the transient neonatal myasthenia gravis.

We report on two interesting cases with a history of neonatal hypotonia and facial weakness with different etiology of neonatal myasthenia.
Case Reports

PATIENT 1

The patient, a girl with Gypsy ethnic origin was born after an uneventful pregnancy, labour and delivery. Her birth weight was 3320 g. Two previous pregnancies of the mother ended with spontaneous abortion. The parents were consanguineous (first cousins). Transient serious hyperbilirubinaemia, caused by Rh incompatibility was observed in the newborn period which needed exchange transfusion. Otherwise her adaptation was uneventful. Bilateral ptosis and weak cry were noticed since early infancy and these symptoms became more obvious later. The patient was referred to us at the age of 16 months with persistent ptosis. On examination hypotonia, bilateral ptosis, limited external eye-movements, myopathic face with constantly open mouth and chewing difficulties were observed. Otherwise the patient’s gross motor and language development was normal; she was able to walk without support and she could speak a few words. The clinical features and the history pointed to a disorder of the motor unit. Screening laboratory tests were in the normal range, serum creatine kinase level was not elevated. Tensilon® (or edrophonium) test was performed under continuous monitoring of the cardio-respiratory parameters and ECG and a positive response was observed: the ptosis improved. Congenital myasthenic syndrome was suspected and molecular analysis was carried out. DNA samples were isolated from peripheral blood leukocytes by the standard salting-out method. Since the deletion in the long of the epsilon (ε) subunit (ε1267delG) is a founder mutation of the cholinergic receptor, nicotinic, epsilon polypeptide gene (17p13.2) for congenital myasthenia in the Gypsy population2, 3 this was the first target in our investigation.

In order to detect the mutation ε1267delG, a 550/549 bp fragment containing exons 11 and 12 was amplified by PCR using primers 5′-cacggagcgagctggttga -3′ and 5′-ctggagatgggtgggaattg-3′4. The ε1267delG mutation results in loss of the XagI site. The mutant allele remains undigested, whereas the wild-type allele yields two fragments (355 bp and 195 bp). Restriction enzyme digestion was carried out at 37°C for 4 h by adding 15 units of XagI in 20 µl of reaction mixture. Restriction fragments were size-fractionated on a 2% agarose gel containing ethidium bromide. In patients homozygous for ε1267delG the mutation was confirmed by direct sequencing the above mentioned PCR product containing exon 11 and 12 of the AchR ε gene. Mutation analysis of the AchR subunit genes revealed a homozygous ε 1267delG in the patient whereas the parents were heterozygous for the same mutation (Figure 1).

On the neurological follow up the ptosis showed moderate improvement with standard AchE inhibitor therapy therefore we continued this medication. Respiratory tract infections were frequent. Generalized muscle hypotonia and weakness persisted.

For neuropsychological testing the Hungarian version of the Stanford-Binet intelligence scale was used. The child was examined in six areas (general intelligence, knowledge, quantitative reasoning, fluid reasoning, visual-spatial processing, and working memory) at the age of five years and eight months and no deficit was found in any of these areas.

She was able to attend school at the age of seven, her education begun in a standard primary school.

Figure 1. Restriction enzyme analysis in a Gypsy family with a child diagnosed as CMS patient (3) and their asymptomatic parents (1 and 2). A PCR fragment of 550 bp (549 bp int he mutated allele) containing exon 11 and exon 12 of the AchR ε subunit was amplified. Restriction digest with XagI yields two fragments of 355 bp and 195 bp for the wild-type ε subunit. The ε1267delG mutation results in loss of the XagI site. Both the wild-type and mutant fragments are observed in the parents, indicating heterozygousity for ε1267delG
The patient, a girl was born from the first uneventful pregnancy after 37 weeks of gestation. Her birth weight was 2490 g. Apgar scores were 10 at 1, 5 and 10 minutes, respectively, however shortly after birth respiratory failure developed. Generalized hypotonia, ptosis, facial weakness, tent-shaped mouth and weak cry were noticed. Mechanical ventilation was not required, however she was not able to swallow her saliva and tube feeding became necessary. Brain MRI was normal, laboratory tests (including screening for inborn error of metabolism) were in the normal range and microbiologic cultures did not reveal CNS infection, or metabolic origin of the symptoms. It turned out that the mother had already complained about fluctuating, generalized weakness and fatigability worsening on exercise, but no detailed check-up was performed until the symptoms of the child were apparent. On examination the mother had generalized weakness, mild bilateral ptosis, mask-like face and slight dysarthria. Based on the similar clinical features of the mother and her newborn the diagnosis of myasthenia gravis was suspected. Anti-acetylcholine receptor antibody was detected in both the mother (5,29 pM) and the newborn (6,03 pM), which result confirmed our suspicion. We concluded that the newborn had transient neonatal myasthenia gravis and her mother had autoimmune myasthenia gravis.

The clinical symptoms of the newborn improved spontaneously. She became bottle-fed and the bilateral ptosis and muscle weakness showed remission. She was discharged at the age of one month without medical treatment. An apnoe alarm monitor was provided for safety reasons. On regular neurological follow up her muscle tone and motor development was normal, ptosis, or bulbar signs were not noticed. She was bottle-fed and had appropriate weight gain.

For neuropsychological testing the Brunet-Lézine test was used at the age of 22 months. Her gross and fine motor functions and social responses were appropriate for her age.

The mother’s condition improved after thymectomy and treatment with a combination of AchE inhibitor and azathioprine.

Discussion

The **congenital myasthenic syndromes** are heterogeneous disorders from the pathological and clinical point of view¹, defined as inherited disorders of the neuromuscular transmission, caused by different mutations of the acetylcholine receptor subunits or different enzyme proteins in the neuromuscular junction. The congenital myasthenic syndromes can be classified according to the site of the defect: presynaptic, synaptic or postsynaptic, or by the inheritance of the endplate-specific proteins’ mutations⁶.

The symptoms usually present at birth or within the first two years of life. During the neonatal period ptosis and facial weakness are common symptoms and respiratory failure is often the most important complication. Later delayed acquisition of the motor milestones and exercise-induced fatigability are characteristic features. The differentiation from other disorders of the motor unit is mandatory⁵.

In some congenital myasthenic syndrome patients the characteristic features of the symptoms point to a specific diagnosis, but in the majority of the cases specific electrophysiologic and molecular genetic studies are required to determine the etiology⁷-⁹. For most of the mutations, well established DNA-based genetic tests are available⁷.

Intravenous edrophonium test can be carried out on infants with suspected myasthenia gravis¹⁰, but this test cannot be recommended for routine use because of risk of side effects. Intramuscular neostigmin in a dose of 0.15 mg/kg seems to be preferred for infants and younger children for testing myastenia¹¹.

Unfortunately in congenital myasthenic syndromes the efficacy of the treatment is usually diminished and the prognosis is less favourable. In the form of presynaptic defects, administration of the cholinesterase inhibitors can be successfully used. In two forms of postsynaptic defects (slow-channel and fast-channel syndromes) there is also a possible effective medical treatment. Administration of long-acting open-channel blocker of the AchR (*quinidin*) is used to normalize the prolonged opening episodes of the mutant slow-channels. Administration of the combined therapy of the cholinesterase inhibitors and the potassium channel blocker (3,4-diaminopyridine-3,4DAP) might be effective in fast-channel syndromes. At the present time no effective therapy is known in the synaptic defect (endplate AchE deficiency) type of congenital myasthenic syndromes¹²,¹³.

In our case homozygous deletion in the long cytoplasmic loop of the ε subunit (1267delG) was the cause of the congenital myasthenic syndrome, which mutation is characteristic for the Gypsy population, or South-Eastern European families. The typical clinical symptoms include presence of ptosis, hypotonia associated with mild to moderate degree of weakness and fatigability of the bulbar...
The transient neonatal myasthenia gravis is clearly related to the dysfunction of the postsynaptic transmission in the neuromuscular junction. In most of the cases IgG type antibodies against the nicotinic acetylcholine receptor (NAchR) are present in the serum of the mother with myasthenia gravis. These anti-NAchR antibodies cross the placenta and bind to the receptors, located on the post-synaptic membrane in the newborn, inhibiting their function\(^4\). Although most infants born to myasthenic mothers possess anti-NAchR antibodies at birth, approximately 10-20\% develop transient neonatal myasthenia gravis\(^5\).

The features of the transient neonatal myasthenia gravis appear shortly after birth, or within the first few days characterized by generalized muscle weakness and decreased muscle tone, feeding difficulties and different severity of respiratory failure. Faint cry-sound, weakness of the facial muscles, ptosis and inability to suck or swallow is also common. No significant connection was found between the seriousness of the clinical features and the level of the mothers’ serum antibodies or the extent of the disease of the mother\(^6\).

Transient neonatal myasthenia gravis is a self-limiting disease, after the antibodies disappear from the blood and muscle tissue, spontaneous remission is expected and the infants become asymptomatic after three weeks\(^7\). Early diagnosis is crucial to decrease the prevalence of life-threatening respiratory complications. Application of supportive treatment such as transient ventilation and nasogastric feeding can be crucial.

Administration of AchE inhibitors for a few days or occasionally for a few weeks is usually necessary but requires special caution in infants, due to the higher risk of cardiac arrhythmic side effects. Plasmapheresis or intravenous immunoglobulin administration is an alternative therapeutic option but results regarding the effectiveness is inconsistent\(^8, 9\).

The real challenge is to establish the early diagnosis when the mother’s disease is not known yet. In this case the symptoms, complaints of the mother and physical examination can provide important diagnostic information. Detection of anti-NAchR antibodies from the plasma and the decrement response during repetitive nerve stimulation confirms the diagnosis.

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