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Case Report

Congenital Myotonic Dystrophy: Rare Cause of Respiratory Distress - Case Reports

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Abstract

Myotonic dystrophy type 1 is multisystemic disease, which is clinicaly manifested with muscular hypotrophy or weakness, myotonia, cataracts, heart rythm and conduction disturbancies, altered function of endocrine glands, disturbances of respiratory and gastrointestinal tract, as well as peripher and central nervous system disorders. DM 1 is inherited in autosomal dominant pattern. It is caused by CTG trinucleotides expansion in the non-coding region of the dystrophia myiotonica protein kinase gene (DMPK), located on the chromosome 19 (19q13.3). There are four main forms of disease according to number of CTG repeats, age of onset and severety of symptoms: Mild (late) adult form, Classical adult form, Childhood/Juvenile form and Congenital form. Congenital myotonic dystrophy has incidence up to 1:47619. It is present at birth, has most severe clinical apearence and highest rate of mortality. We are presenting two cases of congenital DM 1, from the same familiy, hospitalised in our NICU at the same time. Both pregnancies were with polyhydroamnion. Both newborns had severe respiratory distress at birth and later chronic respiratory failure, severe congenital muscular hypotonia, large head circumference, ventriculomegalia and later hydrocephalus. In both cases evident was craniofacial dysmorphia, poor facial expressions, poor spontaneus movements, cryptorchism. Both patients suffer from severe gastroparesis and gastrointestinal hypomotility, which cause poor peroral feeding, and poor weight gain. We determined that both patients were close relatives. Unfortunately all problems that were present at birth got worse, and both patients did not survive infancy.

Keywords: *Congenital Myotonic Dystrophy 1; Respiratory Distress*

Introduction

Myotonic dystrophy type 1 (DM 1) or Steinert's disease is multisystemic slowprogresive disease, which is clinicaly manifested with muscular hypotrophy or muscular weakness, myotonia, cataracts, heart rythm and conduction disturbancies, altered function of endocrine glands, disturbances of respiratory and gastrointestinal tract, as well as peripher and central nervous system disorders.

Disease was first described in 1909. by german profesor Hans Gustav Wilhelm Steinert. He named the disease Myotonic dystrophy, and in his honor later authors used the name Steinert's disease. DM 1 is inherited in autosomal dominant pattern. It is caused by CTG trinucleotides expansion in the non-coding region of the dystrophia myiotonica protein kinase gene (DMPK). This gene is located on the long arm of chromosome 19 (19q13.3). In healthy persons this DMPK gene segment is polimorphous and may have 5 - 37 CTG copies. Diseased individuals have larger number of CTG repeats, and this number can range between 50 to several thousands. Those who have 38 - 49 copies are considered to have premutation, and they are at risc to have offspring with symthomatic disease. Commonly larger number of CTG triplets corelates with severe symptoms and early onset of the disease. This number can vary between the cells in the same person, and can be larger during the years. Important caracteristic of DM 1 is genetic anticipation phenomenon, which means that number of CTG repeats becomes larger in every next generation and therefore gene instability grows up. Unstabile genes with large number of CTG trinucleotides are transfered mainly through mother's ovarian cells, which can cause congenital onset of the disease. DMPK gene caries

information for dystrophia myotonica protein kinase, a protein whose precise function is not well known. It is noticed that this protein has essential role for normal muscular, heart and brain cells function, and it is necessary for comunication and impulse transmition within and between cells. Basic pathophysiological mechanism for the disease is production of mutant DMPK transcript, very stabile and long RNA hairpin structure, so called toxic RNA. This altered RNA is been acumulated in cell nucleus, which causes almost complete block of nuclear export of mutant DMPK transcripts and abberant seqestration of RNA-binding proteins. That explains the multisystemic character of the disease [1,2].

DM 1 has broad spectrum of phenotype manifestations depends on genotype expression. There are four main forms of disease according to number of CTG repeats, age of onset and severety of symptoms: Mild (late) adult form, Classical adult form, Childhood/Juvenile form and Congenital form (Summary of signs and symptomes is given in table 1). The incidence of DM1 in overall population is 1:8000 [3,4]. In Serbia incidence is 1:20000. Congenital myotonic dystrophy has incidence up to 1:47619 [5]. It is presented at birth, has most severe clinical apearence and highest rate of mortality, up to 40% [6].

Phenotype	Number of CTG triplets	Age og onset	Clinical appearance
Premutation	38 - 49	-	-
Late adult (mild) type	50 - 100	40 to 70 years	Mild myotonia
			Cataracts
Clasical adult type	50 - 1000	20 to 40 years	Myotonia
			Muscular weakness
			Muscular hypotrophy
			Cataracts
			Hypersomnia
			Insulin resistance
			Heart rythm and conduction disturbancies
			Respiratory failure
Childhood/Juvenile type	> 800	1 to 20 years	Cognitive defects
			Psychosocial difficulties
			Facial weakness
			Incontinence
Congenital type	> 1000	Birth	Polyhydroamnion
			Reduced fetal movements
			Hypotonia
			Respiratory distress
			Facial dysmorphia
			Contractures
			Feeding difficulties
			Psychomotor retardation
			Cognitive defects

Table 1: *Types of Myotonic dystrophy type 1.*

Case Report

Case 1

Male newly born infant was conceived in third, IVF induced pregnancy. Mother has treated for infertility for 12 years. Pregnancy was well controled, and in 8. month polyhydroamnion is registered. Delivery was made in term (38 week of gestation), with elective cesarean section. Amniotic fluid was abundand and milky. Apgar score was 4/5/6, birth weight 3250gr (P 42), birth lenght 54 cm (P 98), head circumference 38 cm (> P 99). Severe muscular hypotonia was noticed at birth, as well as bradycardia and respiratory distress. Neonatal resuscitation was initiated: aspiration, ventilation, tactile stimulation, one dose of Epinephrine was administrated. After 30 minutes spontaneous respirations were irregular and shallow, newborn was transferred to NICU and mechanical ventilation was started in first hour of life. Detailed clinical examination showed severe muscular hypotonia, absence of reflexes, increased head circumference, prominent frontal eminences, enophtalmus, wide frontal fontanelle, contractures of fingers of the right arm, cryptorhidism. Auscultatory findings were normal. Chest radiography was without significant deviations (Figure 1). Laboratory analises was also whithin the normal range. Echosonography of CNS showed ventriculomegaly (Figure 2). ECG and echocardiography were normal for the age.

At the first visit of newborn's parents we have discovered that the mother of our patient is a carrier of DMPK gene mutation whithin the range of 120 to 200 CTG triplets. She is 40 years old, and strongly denies signs and simptoms of DM 1. We noticed muscular weakness, ptosis, poor facial mimic, nasal speach and slow walk. Mother's sibilings: sister and two brothers have DMPK mutation too (100 to 600 CTG repeats). Presence of the same mutation was found in amniotic fluid cells of the fetus during the pregnancy follow-up. Termination of pregnancy was advised, but the mother refused to do so. Genetic analysis of the newborn was repeated, this time from blood sample, and it was reveald that our patinet has 1700 CTG triplets in DMPK gene, which confirms congenital, severest type of DM 1.

During the hospitalisation mechanical ventilation was performed with low pressures and low oxigen concentration. We have tried on several occasions to wean the patinent from respirator, but every time oxigen saturation was decreased within 10 minutes. Spontaneous breathing was never established. Detailed cardiological evaluation showed normal function of cardiovascular system. In first few days of life we suspected on ileus, but conservative treatment was enough to restore normal defecation. From the very beginig peroral feeding trough nasogastric tube was poor. We manage to increase volume of formula up to 50 ml per feeding, but most of the time peroral intake was poor. We suspected on pyloric stenosis, which was excluded with ultrasound exemination. It was concluded that adequate feeding is not possible due to gastroparesis and intestine hypomotility, disorders that can be present in DM 1. All attempts of peroral feeding as well as parenteral feeding did not contribute to the weight gain. Ventriculomegaly was progresing, hydrocephalus develops, with rare convulsions. Neurosurgeon did not indicated placement of VP shunt. All the time sceletal muscle hypotonia was present with absence of reflexes and rare spontaneous movements, slightly markable on upper limbs. We tried to improve muscular tone with physical therapy with weak success. Facial dysmorphy and absence of mimic were more pronounced with age. Hospital course was complicated with frequent infections despite adequate antibiotic treatment. In age of four months our patinet died.

Case 2

Three months after the hospitalization of the first newborn, second one was admitted with similar clinical features. It was a firstborn male neonate from the first controlled pregnancy. Mother who was 24 years old at the time, was sent to Clinical centre due to polyhydramnios and fetal ventriculomegaly. NMR of fetus was recommended, but mother refused to do it. Mother is denying any illness, but examination revealed bilateral renal stasis, glucose intolerance, high values of transaminases, LDH and Gama-GT. Delivery was made with cesarean section, in 39 week of pregnancy. Birth weight was 4060gr (P 91), birth length 56c m (> P 99), head circumference 39 cm (> P 99), Apgar score 6/7. At birth newborn was livid, hypotonic with shallow and irregular respiration. After aspiration and tactile stimulation breathing was established. With oxygen treatment, oxygen saturation was normal. Three hours after the birth, newborn's condition rapidly deteriorates, breading was irregular, oxygen saturation low. Infant was transferred to our NICU and mechanical ventilation is started. Clinical presentation was similiar as in previous case: severe muscular hypotonia, absence of reflexes, increased head circumference, prominent frontal eminences, hypertelorism, craniofacial dysmorphism, poor facial mimic, high-arched palate, wide frontal fontanelle, cryptorhidism, pes equinovarus bilateralis. Auscultatory findings were without major disrepancies. Chest radiography was normal (Figure 1). Laboratory analises at admission was also whithin the normal range. Echocardiography was normal for the age. Ultrasound examination of CNS showed hzdrocephalus (Figure 2).

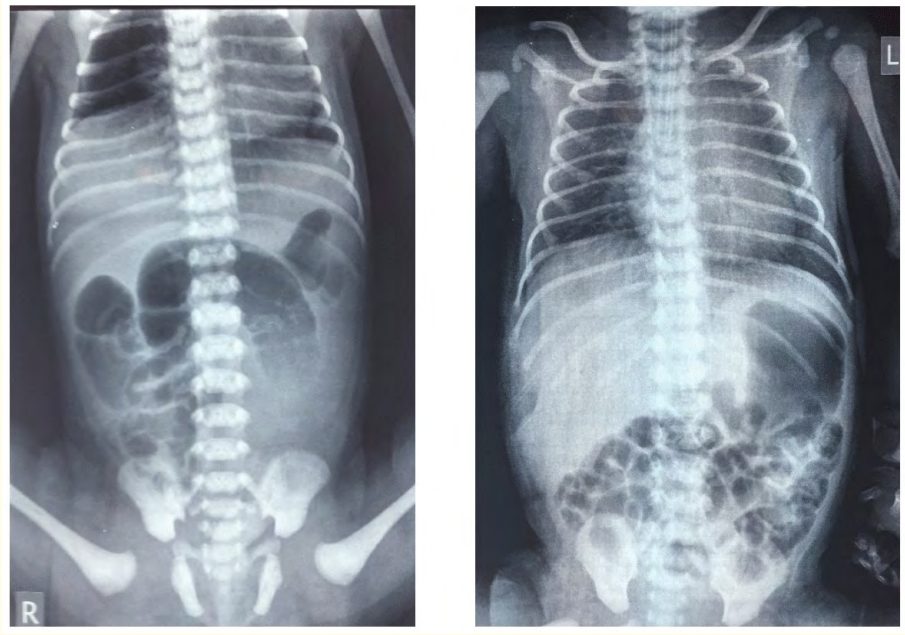

Figure 1: *Babygrams of both patients at admission. Left is case 1, right is case 2.*

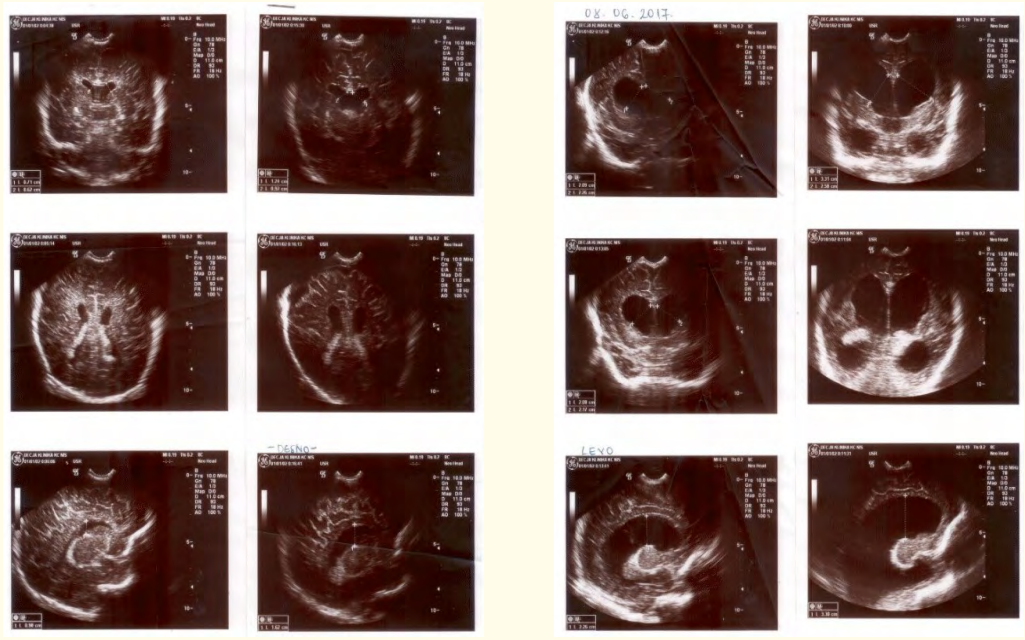

Figure 2: *Brain ultrasound of both cases. Left is case 1, right is case 2. In both cases is evident progression of ventricular enlargment, in case 2 hydrocephalus with rapid progression.*

Similar clinical presentation led us to believe that this patient has the same disease. But DM 1 is not so common disease and what is the possibility to have two patients in the same NICU with same rare diagnosis. Last names of both mothers were different, they were from different cities, their age was different. In the conversation with parents of the second baby, we asked them do they know the mother of the first newborn. We discovered that they were related, that mother of the first child and maternal grandfather of the second child are siblings. This grandfather had DMPK mutation in range of 100 to 220 repeats. Analysis was never performed on his daughter, mother of the second child. We order analysis and it revealed presence of the mutation on both: mother and newborn. Number of CTG triplets was not estimated. Genetic advice was given for prenatal DM1 diagnosis in further pregnancies (Figure 3).

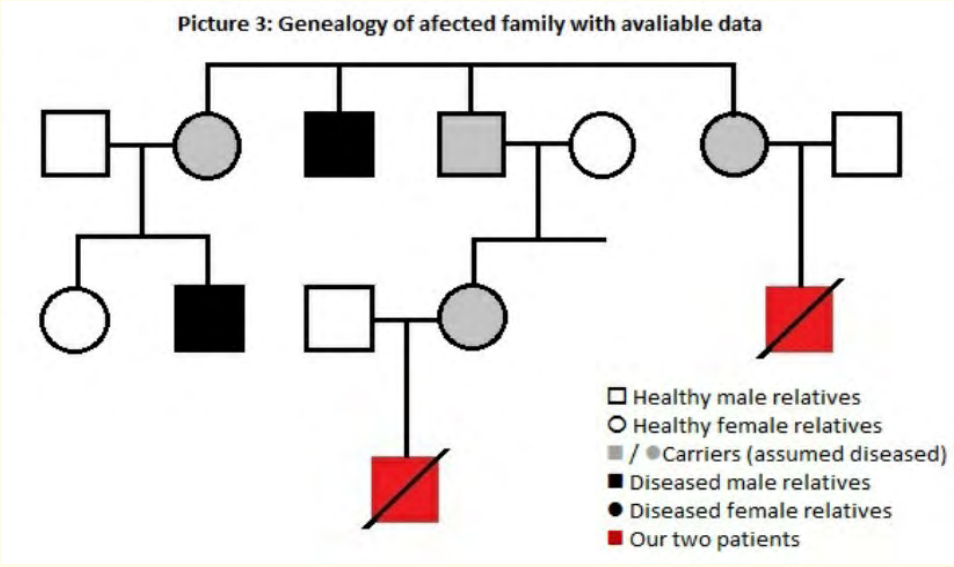

Figure 3: *Genealogy of affected family with available data.*

Mechanical ventilation was conducted with low pressures and low oxigen concentration. Weaning the patinent from respirator, tried on several ocasions, was every time unsuccessful. Oxigen sturation decreased within several minutes. Spontaneous breathing was never established. As in the first case we suspected that patient has ileus, but normal defecation was established. Peroral feeding trough naso-gastric tube was poor. Pyloric stenosis was excluded with ultrasound exemination. Feeding was combined: peroral and parenteral, but the weight gain was very bad. Hydrocephalus was progresing rapidly, much faster then in previous case. Neurosurgeon once again did not indicated placement of VP shunt, due to frequent infections with trombocytopenia. All the time sceletal muscle hypotonia was present with absence of reflexes and rare spontaneous movements. Attepmts to improve muscular tone with physical therapy had no success. Facial dysmorphy and absence of mimic were more pronounced with age. After three months this patient died too.

Discussion

Our patients had Congenital myotonic dystrophy type 1, most severe type of the disease. Respiratory distress at birth and respiratory insufficiency were present in both cases. Although they didn't had cardiopulmonal anomalies, nor serious consequences of mechanical ventilation, severe generalised hypotonia caused serious weakness of respiratory muscules, which led to chronic respiratory insufficiency. Musular weakness, one of the basic signs of the disease in all ages, is accused for contractures (present in case 1) and feet deformity (present in case 2). Feeding difficulties, poor gastrointestinal motility, constipation, which are described in literature along with other gastrointestinal disturbancies [7], were present in both cases. They led to insufficient weight gain and contributed to the unfavorable outcome. Ventriculomegaly present at birth in both cases progressed to hydrocephalus, more rapidly in second case. This is one of the

frequent findings and together with enlarged head circumference and polyhydroamnion can be seen on prenatal ultrasound [8]. Some authors described atrophy of grey and white matter with ventricular enlargment in adult patients who have DM 1 [9,10]. In congenital form, these disturbancies are more severe, hydrocephalus develops early and brain atrophy is significant. This is probably the cause of serious cognitive defects and psychomotor delay in children who are stabilised and managed to survive infancy [5,6]. High rate of mortality, up to 40% is caracteristic for congenital disease, and unfortunatly our both patients contributed to that percent.

Conclusion

Myotonic dystrophy type 1 is rare disease, but after Dushenne and Becker muscular dystrophy, it is one of the leading muscular disorders in childhood. Congenital form of the disease is the severest one, and causes high mortality. Polyhydroamnion, large head circumference and ventricular enlargment can be spoted with prenatal ultrasound. Together with reduced fetal mouvments, this can raise suspicion on DM1, which can be proven prenataly. Severe generalised muscular hypotonia and respiratory distress present at birth must lead physician to think about this disease even when parents deny any signs and symptoms. Genetic counceling and early diagnosis are very important to avoid possible serious consequencies of this rare but still present form of the disease.

Bibliography

1. Konieczny P., *et al*. "MBNL proteins and their target RNAs, interaction and splicing regulation". *Nucleic Acids Research* 42.17 (2014): 10873-10887.

2. Gudde AEEG., *et al*. "Trinucleotide repeat expanded and normal DMPK transcripts contain unusualy long poly(A) tails despite differential nuclear residence". *Biochimica et Biophysica Acta* 1860.6 (2017): 740-749.

3. Delin S., *et al*. "Kongenitalna miotonicka distrofija - prikaz bolesnika". *Paediatria Croatica* 58 (2014): 278-282.

4. Harper PS. "Major problems in Neurology: Myotonic dystrophy, 1st edition". London, UK: W.B. Sounders (2001).

5. Cambbell C., *et al*. "Congenital myotonic dystrophy: Canadian population-based surveillance study". *Journal of Pediatrics* 163.1 (2013): 120-125.

6. Ho G., *et al*. "Congenital and childhood myotonic dystrophy: Current aspects of disease and future directions". *World Journal of Clinical Pediatrics* 4.4 (2015): 66-80.

7. Hageman AT., *et al*. "Congenital myotonic dystrophy: a report of thirteen cases and a review of literature". *Journal of the Neurological Sciences* 115.1 (1993): 95-101.

8. Zaki M., *et al*. "Congenital myotonic dystrophy: prenatal ultrasound findings and pregnancy outcome". *Ultrasound in Obstetrics and Gynecology* 29.3 (2007): 284-288.

9. Zanini S., *et al*. "Relationship of white and gray matter abnormalities to clinical and genetic features in myotonic dystrophy type 1". *NeuroImage: Clinical* 11 (2016): 678-685.

10. Schneider-Gold C., *et al*. "Cortical and subcortical grey and white matter atrophy in Myotonic dystrophies type 1 and 2 is associated with cognitive impairment, depression and daytime sleepiness". *PLOS One* 10.6 (2015): e0130352.

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