WERDNIG-HOFFMANN DISEASE WITH DEXTROCARDIA AT CHILDREN - CASE PRESENTATION

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Abstract

Werdnig-Hoffmann disease or type I spinal amyotrophy is a rare, severe neuromuscular affection, with recessive autosomal remittance, characterized by degeneration of the motor neurons from the anterior medullar horns. Clinic signs start from the first months of life and are characterized by marked hypotonia, with severe evolution towards severe respiratory insufficiency and death. The authors describe the case of the female patient S.R. (F.O. 21718), aged 1, who had repeated admissions between December 2008 – April 2009 at the Pediatric Clinics of the Emergency Clinical Hospital Craiova, for respiratory failure. Despite the complex treatment: volemic rebalancing, nourishment through gavage, antibiotherapy, bronhodilatators, and finally mechanic ventilation, evolution was towards exitus.

Introduction

Progressive spinal amyotrophies represent a heterogenous group of genetic disorders which in the first stage of childhood, characterized by progressive degeneration of the motor neurons from the anterior medullar horn and sometimes, of the motor neurons from the cerebral trunk and is manifested by marked hypotonia.

Today, this group of affections represent the second cause as frequency, of lethal genetic disorder, which begins in childhood, after the cystic fibrosis.

Case presentation

We present the case of the female patient S.R. aged 1, who had repeated admissions in 2009 at the Pediatric Clinics of the Emergency Clinical Hospital Craiova.

From heredocolateral antecedents we learned that a first grade female cousin of her father had a similar disease, dying at 13 years old, and the first child of the couple, also a girl, deceased at 7 months old with the diagnostic Werdnig-Hoffmann disease.

The patient is the second child of a couple of young genitors, coming from a physiologic pregnancy and an eutocic birth, having birth weight 3800g.

The patient S.R. was diagnosed at the age of 2 months with Werdnig-Hoffmann disease – type I spinal amyotrophy. The reasons for her last two admissions in 1st Pediatric Clinic were similar: fever, coughing, tachypnea, moans, epigastric and intercoastal tirage, deglutition turbulences.

At the objective examination we noticed: deficitary nutrition status, weight 6000g (grade II dystrophy), severe neuromotor retardness, feeble screams, generalized muscular hypotonia, characteristic position of the members in abduction, "bell-like" aspect of the chest, toracoabdominal balance (paradoxal breathing), breathe rate 56/min, pulmonary stet acoustic crepitant waves, tachycardia (heart rate 116-130b/min), apexian shock in the right part of the breastbone, liver with the inferior edge 1 cm under ribs boundary, normal limits spleen, tongue fasciculations with severe difficulties in nourishment, absence of ROT.

Neurologic examination: infant with extreme hypotonia and proximal motor deficiency, segmented active movements possible only distal with reduced amplitude, tongue fasciculations, paradoxal breathing. She didn't sit, didn't emit syllables, absence ROT, late response at tactile stimulus, soft nape, absent meningeal syndrome.

Paraclinic investigations: hemoglobin 10,4g/dl, hematocrit 31%, platelets 363000/mm^3, leucocytes 5100/ mm^3, neutrophils 46%, lymphocyte 45%, monocyte 9%, ALT 14,8U/l, AST 4U/l, urea 30mg/dl, amylase 31U/l, creatinine 0,1mg/dl, total bilirubin 0,3 mg/dl, glycemia 116mg/dl, alkaline reserve 20mEq/l.

Thorax radiography: thoracic asymmetry, peribronhovascular interstitial opacities; trachea movement, mediastinum, cardiac shadow towards right.

At the first admission she received treatment consisting of antibiotics, bronhodilatators, oxygenotherapy using mask, nourishment through gavage, then oral. She was discharged with improved general status, diminished breathing failure syndrome, present appetite.

After 2 days from discharging, she was readmissioned with the symptomatology of an aspiration bronchopneumonia, extremely grave general state, grade I/II coma.

She was supervised in the Intensive Therapy Clinic where she was intubated oro-tracheal and mechanical ventilated, hydroelectrolitical and acidobasic rebalanced, treated with antibiotics, simptomatics, but the general state gradually got worse, presented signs of decerebration, and in the 9th day since admission, irreversible cardiac arrest.

At the necroptic examination, the aspiration bronchopneumonia and dextrocardia were confirmed.

Discussions

Depending on the age it began and the grade of severity of the disease, there are described four types of spinal amyotrophy: type I, Werdnig-Hoffmann disease or the severe infantile acute form, type II or the infantile cronic

form, type III or Kugelberg-Welander disease or the juvenile form and type IV with the beginning at adult stage. All types are determined by recessive mutation on the SMN1 gene (survival motor neuron).

Werdnig-Hoffmann disease or type I is the most severe form of spinal amyotrophy, present only at the infant and little child; it is a rare, progressive neuromuscular disease, characterized by the degenerescence of the motor neurons.

The frequency of the disease is 1/25 000 births. The pathogenic layer seems to be, after the latest studies, a process of apoptosis or programmed cellular death. In over 95% of the cases the affection is determined by deletions or anomalies of the SMN1 gene from the cromozome 5, training a major deficit of the SMN protein. Genetic studies linked this affection to the the cromozome 5q11.2-q13.3, the same region being affected by spinal amyotrophy types II and III. The disease has ereditary transmission of recessive autosomal type. The deletion of the NAIP gene (Neuronal Apoptosis Inhibitory Protein) is also associated with the spinal amyotrophy (4,9).

The cause of the disease is a defective gene. All humans are born with many extra neurons which are genetically programmed to die successively. Healthy children have a gene capable to communicate to the body the moment when sufficient nerve cells have died. Children with the Werdnig-Hoffmann disease don't have this gene and the nerve cells continue to die until the organism and especially the muscles are severily injured.

Other authors reached the conclusion that the axonogenesis defects represent the major cause of spinal amyotrophy, which could leads to new therapeutic options in neuromuscular diseases (5).

Some studies proved the existence of a link between the starting age and the decease age; so, the patients with the disease starting age of under 2 months had a severe prognosis, with a sooner decease, compared to the ones who had a somehow later starting age but who met the diagnostic criteria for the type I disease (8).

At the presented case, the clinic signs which suggested the early diagnostic were: hypotonous newborn, with nourishment and respiratory problems. After 2 months the neurologic examination confirmed the diagnostic of Werdnig-Hoffmann disease. It was noticed that she can't hold or turn her head. The limbs' aspect was revealing: infant with "batrachian" characteristic position, with thighs in abduction and external rotation, arms in abduction and internal rotation, and forearms in pronation. Also she had generalized hypotonia, muscle atrophy, hypokinesis, paralysis at the members' roots, slow movements in joints; irregular breathing, "bell-like" aspect of the chest, slow movements of the fingers, tongue fasciculations, balanced head.

In evolution, appears the paralysis of the intercoastal muscles and of the abdominal muscles. As a consequence the child presents feeble screams, rough and inefficient coughing, anomalies of the active breathing kinetics. When inspiring, the thoracic wall depresses because of the paralysis of the intercoastal muscles and the abdominal wall curves under the pressure of the diaphragm (the only spare muscle) because of the paralysis of the abdominal muscles. Also phonetic and deglutition turbulences appear.

The diagnostic was evoked by the presence of a motor deficit with proximal and symmetric predominance, associated with an amyotrophy, ROT absence and muscular fasciculations presence.

The electromyogram (EMG) and the study of nerve flow speed shows a table of denervation, which allows seeing the difference between a spinal amyotrophy and a sense-motor periferic neuropathy.

The muscular biopsy shows fascicular neurogenous atrophy, at the optic microscope. At the electronic microscope one can notice the predominant touch of the miofibrils with the loss of filaments and the diminishing number of mitochondria. Biopsy is not needed if the genetic diagnostic is made.

The association of the dextrocardia at the presented case is a rare association which I couldn't find in the literature.

From the literature, some studies concluded that the heart congenital malformations are caused by major deficits of the SMN protein. The authors met most frequently atrial and ventricular septal defects, but also other minor cardiac anomalies, like the oval foramen persistency or the arterial channel persistency. It was also noticed that on the patients with associated cardiac malformations, the evolution of the neuromuscular affections was more severe (7).

A curative treatment of the disease doesn't exist, only the intercurrent infections are treated. The physiotherapy can't increase the life of these children over 18 months. The devices that help in alimentation, the gastrostome or nazogastric sonds, the mechanical ventilation, which is used in terminal cases, can reduce the decease risk, increasing the survival time (6).

Other studies specify that the treatment with salbutamol determines the increase in level of the SMN protein, in researches done on fibroblasts from patients with spinal amyotrophy type I, II and III (1). Other authors reported the generation of pluripotent stem cells inducted from samples of fibroblastic cells from skin from a child with spinal amyotrophy type I (3).

The genetic advice is necessary in all cases and especially at the mentioned couple. Each parent is heterozygote for the pathologic recessive gene. The prenatal diagnostic is possible and is done directly, analyzing the 7^{th} exone of the SMN gene (the search for a homozygote deletion), analysis of the polymorphic markers which flank the genetic anomaly (C212 and C272); the indirect method permits the exclusion of an eventual maternal contamination and the detection of an eventual new mutation .

The particularity of this couple of heterozygotes is that they had, one after another, two daughters with the Werdnig-Hoffmann disease without recognizing that they are cosanguineous. At the analized patient the dextrocardia was associated with the Werdnig-Hoffmann disease.

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