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A Deficit of ATP-ase Subunit 8: with Contribution for Two New Cases

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Summary: In two consanguineous children brother and sister were reported rare mitochondrial disorder caused by mutation of the gene of MT-ATP8: base change T8412C, with aminoacid change: methionin - threonine which wasthe cause for decreased activity of the synthesized protein /enzyme/ and to dysfunction of central nervous system and muscle of the affected children. These cases give us the base to recommend children with muscle hypotonia, mental retardation with unknown cause to be hospitalized in Clinical genetics for confirmation of the diagnosis and careful genetic consultation. The foundation of new rare mitochondrial disease of ATP synthase subunit 8 deficiency is useful in Pediatrics and permit treatment and prenatal diagnosis of the family.

Keywords: Mitochondrial Diseases, ATP-ase Subunit 8 Deficit, Mitochondrial DNA Mutation/MT-DNA Mutation/.

1. INTRODUCTION

The mitochondrial diseases have been considered for long time to belong to the group of neuromuscular diseases. The oxidative phosphorilation and the ATP synthase are accomplished not only in the neuromuscular system but in all other organs and systems which contain mitochondria and cause multiorgan clinical symptoms. They are inherited in all possible ways of inheritance [1]. The complex V or the ATP-synthase of mitochondria contains 10-16 subunits, which are coded by the nuclear DNA and 2 subunits 6 and 8, coded by the mitochondrial DNA [2] from nucleotides 8366-8572. The first cases with deficit of ATP-ase are reported by de Coo and al. 1996. In Bulgaria are reported 6 children with this disease by [2, 5, 6]. In all our cases to the moment are discovered new still not announced and still not registered mutations. In one of the cases was discovered a combination between ATP6 and ATP8 gene mutations. A similar case was described by [3].

A unique mutation of the ATP8 is not still described in the literature. The clinical picture of this disease is still unknown.

The aim of our work is to make a phenotype/genotype correlation in children with mutation of ATP8.

2. MATERIALS AND METHODES

The authors report 2 children brother and sister, patients of Clinical Genetics University Children`s Hospital "St Eudokia" and "Alexandrovska", Sofia. The following investigation has been proceeded: clinical investigation, anthropometry, anamnesis, family history, neurological, psychological examination, Roentgenography, EEG, EMG, Transfontanel sonography, CAT, MRI, Echocardiography, abdominal echography.

The following laboratory investigations was carried out: ammonia, lactate, glucose, blood gases, ketobodies, special metabolic investigations: aminoacids by HPLC in Central Genetic Laboratory, Sofia, organic acid and selective metabolic screening – GasMass Spectrometry, Tandem Mass spectrometry in Metabolic Laboratory /Freiburg/, karyogrammes. The mitochondrial DNA was investigated in peripheral venous blood, sequencing of mit. DNA with PCR SBT-method. For analysis of the results were used mathematical statistics methods.

3. RESULTS

A report of the two cases:

1. Clinical case 1:

T. K. V. date of birth 03.03.2001, History of disease 346/06, 5 year`s and 10 months old born from first pathological pregnancy of a mother with high blood pressure and normal delivery. The weight at birth was 3200 gr and height 51 cm. Normal perinatal period. After birth it manifested hypotonia and psychomotor retardation. He was directed at one year`s old from the Center for rehabilitation, Sofia to Clinical Genetics for diagnosis. The diagnosis was Malformative syndrome and psychomotor delay. The child proceeded continuous rehabilitation but despite it he could not walk alone, can not speek.

In the last months before the hospitalization he became more unquiet, he cried at night but he slept well. Sometimes he laughed without a reason and bended forward his body. He had hypersalivation. The child was hospitalized in Clinical genetics for further investigations with dolichocephaly with protruding methopic sutura, with normal cardiorespiratory status. The neurological investigation showed muscle hypotonia, without changes of the reflexes with not permanent hypersalivation, he could not walk alone, when set up straight he hadn`t equilibrium, he could sit in his bed. The investigations showed normal karyogramme, normal selective screening for metabolic diseases, normal dihydropterin reductase, pterines, neopterin, biopterines, biopterin/neopterin index. In the investigation of mitochondrial DNA were not discovered mutations for MELAS, MERRF, NARP, Leigh. It was established a base change T8412C in MT-ATP8 gene, leading to aminoacid change methionin-treonin. The mutation is not still announced in the official base data www.mitomap.org and the importance for the mitochondrial function is still unknown. A treatment was started with high doses of vitamins, carnitin, Q10. The clinical investigation continues.

2. Clinical case 2:

R. K. V., 11month`s old, sister of T. K. B. Before the pregnancy was proceeded genetic consultation in relation with the first sick child, which diagnosis was Malformative syndrome and delay in the psychomotor development. The conclusion was that there is little genetic risk for the birth of second child with the same disease. R. K. V. is born after a second pathological pregnancy, during the last month the mother had oedema. The child is born with sectio Caesarea with weight at birth 3450 gr and height - 50 cm. At the first day she was treated with phototerapy. At the age of 3 months she was consulted with neurologist because of a delay in the psychomotor development and rehabilitation has been started. The child had had a control of the head at 6 months, at 8 months he had had control of the legs. She was hospitalized for investigation in Clinical genetics. She had muscle hypotonia, normal reflexes with normal cardiorespiratory status and abdominal organs. She couldn`t follow with eyes for long. The EEG showed (Fig. 1) diffuse nonspecific changes of teta waves. EMG-without data for segmental demyelinization. The selective screening for metabolic diseases was

normal. The peripheral blood for dehydropteridinereductase, pterines, biopterines, neopterin and biopterin/neopterin index showed normal result. In the investigation of mitochondrial DNA were not discovered mutations for MELAS, MERRF, NARP, Leigh. It was established a base change T8412C in MT-ATP8 gene, leading to aminoacid change methionin-treonin. The mutation, the same like her brother`s, is not still announced in the official base data www.mitomap.org and the importance for the mitochondrial function is still unknown.

In both consanguineous children were found identical results of the mitochondrial mutation, concerning the ATP 8 subunit gene. Their clinical picture is identical and is dominated by neurological symptoms, including muscle hypotonia without data for segmental demyelinisation. The EEG shows diffuse changes of teta type, delay in the psychomotor development of both children. CAT shows atrophy of the brain of the first child. In both children there is identical mutation of ATP8, which most probably concerns all energic processes and in the case the muscle system and the function of central nervous system. The investigation of the mother showed the same mutation which will help the prenatal diagnosis in future pregnancy.

4. DISCUSSION

The authors report a rare mitochondrial disease, concerning the gene of ATP-8. The gene mutation is connected with a base change leading to aminoacid change, which is the reason for the change of the function of the synthesized protein/enzyme/ and to changes in his function in the central nervous system of both children. A similar case was reported by [3] and in their case too were discovered mutations of ATP6 and ATP8. The course of the disease showed neuromuscular involvement and atrophy of the optical nerves which is most probably due to mutation of ATP6 gene, which is established in our patients with this mutation [4, 5]. A treatment to this rare disease is unknown. The multivitamins therapy, replacement therapy with carnitine aims to stimulate the enzyme processes and compensatory to increase the ATP by other alternative ways of metabolism. After a continuous treatment we can make an evaluation of it.

5. CONCLUSION

In children with muscle hyptonia, delay in the psychomotor development with unknown reasons the children must be directed to Clinical genetics for careful and correct proceeding of the genetic consultation. The report of this new mitochondrial disease of ATP synthase subunit 8 is a contribution for Pediatrics and permit a treatment and prenatal diagnosis.

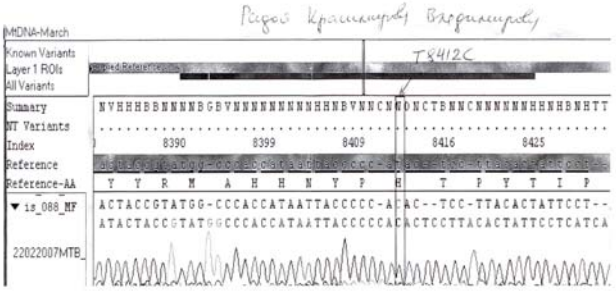

Fig. 1.

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