World Journal of Pharmaceutical research

Volume 3, Issue 2, 2226-2231. Research Article ISSN 2277 – 7105

ROLE OF EARLY INTERVENTION IN A FAMILY OF AFFECTED SIBLINGS WITH SUSPECTED MITOCHONDRIAL DISORDER

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Article Received on
26 November 2013
Revised on 21 December 2013,
Accepted on 18 January 2014

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ABSTRACT

It is important to diagnose and treat inborn errors of metabolism (IEM) patients early as some disorders cause irreversible neurodamage. As most of the disorders are autosomal recessive having 25% chance of recurrence, study of family history may give valuable information. Mitochondrial disorder is a common IEM which may have myopathy as sole or main symptom. The symptoms are mainly because of deficiency of energy production. Diagnosis requires biochemical and molecular analyses which are not easily available, not affordable or not reliable. As there is no single serum biomarker for diagnosis, picking the respiratory chain disorder is challenging. Here we are discussing about a male baby born to consanguineous parents having two affected siblings with possible respiratory chain defect. Blood investigation revealed metabolic acidosis, elevated lactate and lactate: pyruvate ratio. With this background considered patient was suspected to have respiratory chain disorder and treated with Thiamine and Riboflavin which has prevented possible neurodamage.

Key words: Mitochondrial disorder, lactate: pyruvate ratio, thiamine, riboflavin.

INTRODUCTION

Mitochondrial disorder is associated with variable clinical symptoms and may involve multiple organs. It is caused by the pathologic dysfunction or deficiency of enzymes of respiratory chain. Mitochondrial proteins are encoded both by mitochondrial and nuclear DNA. A mutation in the genes which codes these proteins leads to the disorder. It may be either due to mutations in mitochondrial or nuclear DNA. So the inheritance of mitochondrial disorder may be either autosomal recessive, dominant, X-linked, maternal or sporadic pattern(Das et al. 2010). Epidemiological study of childhood and adult population reveals that prevalence of mitochondrial disorder is 1 in 5,000 or even more. However many patients are left undiagnosed due to lack of awareness and non-availability of laboratory facility(Schaefer et al. 2004, J. Kim et al. 2008).

Algorithms available for diagnosis of mitochondrial disorder integrate clinical, biochemical, histological and molecular findings. The disorder may present at any age. Muscle weakness, cardiomyopathy, neurodegeneration, ptosis, hypotonia, myoclonus seizures are some of the clinical symptoms which warrant initiation of baseline workup for mitochondrial disorder (Haas et al. 2007).

Blood lactate, pyruvate, alanine and lactate: pyruvate ratios are the less invasive biochemical markers. Lactate a product of glucose metabolism accumulates due to impaired aerobic metabolism which involves mitochondria. Elevation of lactate and lactate: pyruvate ratios are the nonspecific but important marker for mitochondrial disorder. Estimation of these markers requires proper collection and handling of blood samples. However confirmation of disorder requires invasive tests which include muscle biopsy, enzyme assay and molecular analysis. Clinical presentation is variable and there is no single reliable biomarker for diagnosis and hence picking the case is a challenging task for physicians. Giving proper awareness to primary care physician about manifestations of the disorder may facilitate proper diagnosis (Haas et al. 2007), (Arnold Munnich, 2006).

Treatment for mitochondrial disorder includes symptom based management, reducing the mitochondrial toxin which usually increases during stress conditions like infection, surgery or dehydration, or maintaining optimal health by using preventive measures like antioxidants which reduces free radicals. Riboflavin is a water soluble vitamin B which acts as cofactor for many reactions involving fatty acid oxidation and respiratory chain. Reactive oxygen species are produced in increased amount in mitochondrial disorders and can be reduced by

treating with antioxidants. Hence thiamine one of the antioxidants is used alone or as part of antioxidant cocktail to treat mitochondrial disorder (Parikh et al. 2009). Thiamine deficiency affects complex I activity of respiratory chain, supplementation of which helps in restoring it (Scharfe et al. 2000). Here we are presenting a case of child with history of affected siblings suspected to have mitochondrial disorder and abnormal basic metabolic workup, treated with Thiamine and Riboflavin which has prevented possible neurodamage.

Case report

Present boy is the 3rd child of a consanguineous couple referred to outpatient unit of pediatric department at 6 days of life due to the history of affected siblings with developmental delay. Detailed family history of parent with affected children prevented possible neurodamge in the 3rd child, as family history with affected siblings warranted further workup and treatment.

Mother was referred to the pediatrician at 2 ½ months of pregnancy along with the second child in view of history of two affected female children. History and clinical examination of siblings revealed an initial developmental delay in both and developmental regression in the first child following seizures with involuntary movements and inability to walk. Both siblings were having ptosis, wasting of the small muscles of the hand with normal upper limb and just elicited lower limb reflexes. Many of the energy metabolic disorders leads to myopathy and for some therapeutic options exists (Das et al 2010). In view of absence of perinatal insult and two siblings affected, parents were advised to come for metabolic work up. However they came when the 3rd child was 6 days old and all the three underwent basic metabolic work up. Basic workup in all the three revealed elevated lactate and lactate: pyruvate ratio (Table 1).

Urine metabolic screening was positive for tyrosine and methylmalonic acid. Elevated tyrosine was confirmed by urine GCMS. Elevations of amino acids like glycine, tyrosine, proline and sarcosine, organic acids like intermediates of tricarboxylic acid cycle, methylmalonic acid, methylglutaconic acid and dicarboxylic acids in blood, urine, and CSF have been described in mitochondrial respiratory chain disorders. Elevated lactate: pyruvate ratio is one of the biomarker for respiratory chain disorder (Suomalainen 2011)(Haas et al. 2008)(Arnold Munnich 2006) and hence child started on thiamine and riboflavin. During review, blood investigation showed normalization of lactate and lactate: pyruvate ratio. This made us to continue the therapy. Presently patient is asymptomatic, good in studies with normal motor and mentalmilestones at 4 years of age.

Table1: Basic metabolic work up

	I sibling	II sibling	Present baby	Normal range
Lactate (mg/dl)	67.8	39.5	42.8	less than 20
Pyruvate (mg/dl)	0.1	1.2	0.7	0.2-1.0 mg/dl
Lactate: pyruvate ratio	678	33	60	less than 25

DISCUSSION

Clinical presentation and age at onset is variable for mitochondrial disorder, one of the common IEM and may involve many organs(Skladalet al. 2003)(J. T. Kim et al. 2009). Diagnosis is challenging as there is no specific single serum biomarker for identifying them. A clinical symptom with involvement of more than one organ makes it easy to suspect. As most of the IEMs are hereditary, careful history of siblings may give valuable clues and warrant further work up. Number of algorithms are available which require biochemical, molecular and histopathological examinations which are expensive, not affordable or not easily available (Ficicioglu et al. 2009). Blood gas analysis, lactate and lactate: pyruvate ratio are the basic less invasive and easily available biochemical parameters (Shaham et al. 2010). A severe deficiency in the enzymes of the respiratory chain can lead to accumulation of upstream substrates such as lactate, which is considered as a neurotoxic agent. Clinical suspicion and careful family history are the valuable clues to refer such children to clinics with higher facilities. Mitochondrial disorders occur at any age and damage any organ. Elevated lactate: pyruvate ratio in the affected siblings and in the asymptomatic child made us to consider the present case as mitochondrial respiratory chain disorder. There is no proven treatment for primary mitochondrial disease. Succinate, riboflavin, thiamine, and coenzyme Q10 participate as cofactors in the electron transport chain enzymes((Parikh et al. 2009). Supplementation of these thought to enhance the activity of the enzymes when they are deficient. In a critically ill infant, aggressive treatment before the definitive confirmation of diagnosis is lifesaving and may reduce neurologic sequelae(Raghuveer et al). Complex I form of mitochondrial disorder responds good with riboflavin treatment (Ogle et al. 1997).

CONCLUSION

We conclude that treating asymptomatic children with abnormal basic metabolic work up and family history of affected siblings may help in preventing neurodamage when no other confirmative diagnostic analysis available. Therefore basic workup and discussion with parents by the primary health care providers is warranted when there is strong family history

of affected siblings or sibling death with clinical symptoms such as truncal muscle weakness, hypotonia, cardiomyopathy, involvement of liver and may help to initiate early intervention. Early recognition followed by prompt treatment may prevent progressive neurological damage.

Ethical clearance: Ethical clearance obtained from Institutional Ethical committee (IEC 124/2009).

Informed consent: Informed consent was obtained from the parents of the patient for being included in the study.

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