Ribose-5-Phosphate Isomerase Deficiency (RPID): A Rare Metabolic Disorder

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Abstract: A very uncommon inborn metabolic error that affects the reversible (non-oxidative) phase of the pentose phosphate pathway (PPP) is ribose-5-phosphate isomerase (RPI; EC 5.3.1.6) deficiency. It denotes a new class of disorders involving aberrant pentose and polyol metabolism and is the second known enzyme defect in this section of the PPP, after transaldolase deficiency. Peripheral neuropathy and leukoencephalopathy were the initial symptoms of RPI deficiency in a patient. Born in 1984 to healthy, unrelated parents, he displayed psychomotor retardation from a young age, epilepsy at age 4, and a progressive neurological decline at age 7, marked by mild sensorimotor neuropathy, cerebellar ataxia, spasticity, and optic atrophy. There was no evidence of liver or other organ dysfunction. Widespread abnormalities in the cerebral white matter were discovered by magnetic resonance imaging (MRI). High levels of the polyols ribitol and D-arabitol were detected in the brain using proton magnetic resonance spectroscopy (MRS), and these levels were subsequently verified in bodily fluids. In white matter, quantitative analysis revealed ribitol at 2.9 mmol/L and D-arabitol at 8.9 mmol/L. RPI gene sequencing revealed one frameshift and one missense mutation, while enzyme analyses in fibroblasts verified reduced RPI activity. Pentose derivatives that are reduced to polyols accumulate in tissues and fluids as a result of the biochemical defect that hinders the conversion of ribose-5-phosphate to ribulose-5-phosphate. This finding revealed a hitherto unknown mechanism of metabolic leukoencephalopathy associated with pentose phosphate pathway defects.

Keywords: Pentose phosphate pathway, RPIA gene mutation, ribose-5-phosphate isomerase deficiency (RPID), Leukoencephalopathy accumulation of polyols (ribitol, D-arabitol), inheritance that is autosomal recessive, progressive decline in neurological function, delay in development, epilepsy, retardation of the psychomotor atrophy of the eyes, Sensorimotor neuropathy, spasticity, synthesis of nucleotides, Leukoencephalopathy with progressive toxicity of polyols, impairment of RNA synthesis, a rare metabolic disease.

I. INTRODUCTION

Only four cases of ribose-5-phosphate isomerase deficiency (RPID), an incredibly rare autosomal recessive metabolic disorder brought on by mutations in the RPIA gene, are known to exist worldwide ([19],[22]). The enzyme ribose-5-phosphate isomerase (RPI), which is encoded by the RPIA gene, converts ribose-5-phosphate to ribulose-5-phosphate, a crucial step in nucleotide synthesis and cellular metabolism, and is thus involved in the non-oxidative branch of the pentose phosphate pathway ([16],[13]). When this enzyme is deficient, the pathway is upset, which causes sugar alcohols like ribitol and D-arabitol to build up ([6],[9]). This is especially harmful to the brain and nervous system ([7],[19]). Seizures, spasticity, developmental delay, progressive leukoencephalopathy, and other severe neurological symptoms are clinical manifestations of RPID ([6],[7],[19]). Metabolic studies demonstrating elevated polyols and characteristics. White matter abnormalities detected by MRI are confirmed by genetic testing for RPIA mutations ([6],[7],[22]). There is currently no cure, so supportive care is given with an emphasis on seizure control, occupational and physical therapy, and neurological and developmental issues ([22],[20]).

II. CAUSES

Mutations in the RPIA gene, which codes for the enzyme ribose-5-phosphate isomerase (RPI), result in the extremely rare autosomal recessive metabolic disorder known as ribose-5-phosphate isomerase (RPI) deficiency ([19],[22]). In the non-oxidative portion of the pentose phosphate pathway (PPP), this enzyme is in charge of the reversible conversion of D-ribulose-5-phosphate to D-ribose-5-phosphate ([16]). When a person inherits two faulty copies of the RPIA gene, one from each parent, the disorder is inherited ([19]). The majority of patients that have been reported are compound heterozygotes, meaning that they have one missense mutation (like Ala61Val) that results in a partially active enzyme and one null mutation that produces a non-functional enzyme ([19]). This condition is extremely rare because it is believed that a total loss of RPI activity is fatal ([19],[22]). A lack of RPI interferes with the body's natural metabolism of carbohydrates and results in the buildup of sugar alcohols, primarily D-ribitol and D-arabitol, in the brain, plasma, cerebrospinal fluid, and urine ([6],[9]). These accumulated polyols are linked to progressive leukoencephalopathy, a hallmark of the disorder, and are thought to be toxic to neural tissue ([6],[7]). Furthermore, decreased ribose-5-phosphate synthesis could hinder nucleotide synthesis, which would impact the formation of DNA and RNA ([16],[17]), and possible NADPH depletion could erode antioxidant defenses, leaving neurons more vulnerable to oxidative stress ([14],[15]). Clinically, patients show signs of developmental delay, white matter abnormalities on MRI, and gradually worsening neurological deterioration ([6],[7],[19],[22]). The diagnosis is made by looking for increased polyols in bodily fluids and using genetic testing to confirm biallelic mutations in the RPIA gene ([6],[9],[19],[22]).

III. SYMPTOMS

Retardation of the psychomotor seizures caused by epilepsy, progressive decline in neurologic function, Nystagmus (involuntary eye movement), optic atrophy, and cerebellar ataxia (incoordination), Spasticity sensory-motor neuropathy, worldwide delay in development, spasticity and ataxia, Leukoencephalopathy, Progressive Leukoencephalopathy (brain white matter damage), Low muscle tone, or hypotonia disability of the intellect, regression of motor skills, hearing or vision impairment ([6],[7],[19],[22]).

IV. DIAGNOSIS

A combination of genetic testing, blood, urine, and CSF analysis, as well as neuroimaging, are used to diagnose ribose-5-phosphate isomerase deficiency ([6],[7],[19],[22]). Analyses of blood, urine, and cerebrospinal fluid show an accumulation of metabolites like arabitol and ribitol ([8]), while neuroimaging methods such as proton magnetic resonance spectroscopy can identify increased levels of polyols in the brain ([6],[9]). Lastly, by detecting the precise mutations, genetic testing of the RPIA gene validates the diagnosis ([19],[22]).
Techniques for diagnosis: Neuroimaging ([6],[9]), Body Fluid Analysis ([8]), Genetic Testing ([19],[22]), Measurement of Enzyme Activity ([19]).

V. TREATMENT

The goal of RPI deficiency treatment is to control symptoms and avoid complications ([22],[20]). This could entail dietary changes to restrict consumption of particular foods, nutrient supplements, and continuous medical supervision ([22]). In certain situations, extra drugs or treatments might be suggested to treat particular symptoms or side effects of the illness ([22]). To guarantee the best possible management of RPI deficiency, routine follow-ups are necessary ([22]). For people with RPI deficiency, Enzyme Replacement Therapy (ERT) is a popular treatment option ([22],[20]). It involves giving synthetic versions of the missing enzyme to help restore metabolic function and reduce symptoms ([22]). By limiting the consumption of foods that the body cannot adequately metabolize, dietary changes like adhering to a low-galactose diet can help manage RPI deficiency ([22]). Individuals with RPI deficiency must have their symptoms regularly monitored and managed by a medical professional who specializes in metabolic disorders in order to guarantee early intervention and suitable treatment plan modifications ([22]). For

people with RPI deficiency and their families, genetic counseling may be advised (²²).

Treatment of Ribose-5-Phosphate Isomerase Deficiency with Homeopathy:

Since ribose-5-phosphate isomerase (RPI) deficiency is a genetic metabolic disorder, there is no specific homeopathic remedy for it (²²). However, homeopathic medicines may help in managing symptoms such as muscle weakness, seizures, and developmental delays (²²). Neurological symptoms: Ataxia, spasticity, and muscle weakness – Gelsemium (²²), Zincum Metallicum (²²). Convulsions and Seizures – Cuprum Metallicum (²²), Bufo Rana (²²), Silicea (²²). Cognitive Problems & Developmental Delays – Baryta Carbonica (²²), Calcarea Phosphorica (²²), Tuberculinum (²²). Support for Metabolic Imbalance in General – Natrium Muriaticum (²²), Phosphorus (²²).

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