Review Article

# RIBOSE 5 PHOSPHATE ISOMERASE DEFICIENCY: A RAREMETABOLIC DISORDER

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**ABSTRACT**:

An enzymopathy of the pentose phosphate pathway is ribose 5-phosphate isomerase (RPI) deficiency. One rare condition that no medication can prevent is ribose 5-phosphate isomerase. These diseases, which cause the brain's mucus and white matter to build abnormally and impair brain function, are the most underappreciated. And as a result, people pass away. In this condition, the amount of cerebral white matter increases and decreases, elevating the D-ribitol level. Residue exchange cannot be entirely blamed for the RPI activity observed in patient cells. The rarest conceivable disease, ribose-5-phosphate isomerase deficiency, is a malfunction in the pentose phosphate pathway (PPP) with only one confirmed case. Because ribose-5-phosphate isomerase is an enzyme involved in the pentose phosphate pathway, mutations in this enzyme can cause ribose 5 phosphate isomerase deficiency, the most uncommon condition. Ribose 5 phosphate utilizes the purine synthesis pathway to initiate the production of phosphoribosyl pyrophosphate (PRPP). Ribose and ribose phosphate are the products as well as the intermediates of the pentose phosphate pathway.A fairly uncommon, hereditary pentose phosphate metabolism condition called ribose-5-P isomerase deficiency is characterized by a progressive leukoencephalopathy and significantly elevated levels of ribitol and D-arabitol in the brain and bodily fluids. Unstable ribose 5 phosphate enzyme synthesis is the cause of ribose 5 phosphate isomerase. Any disease that affects the human body, such as optic atrophy, cerebellar ataxia, seizures, or epilepsy, is the cause of them. Treatment for diseases resulting from ribose 5 phosphate isomerase problem is utilized to diagnose them.

**Keywords:** ribose-5-phosphate isomerase deficiency, rare metabolic disease, carbohydrate metabolism, pentose phosphate pathway.

## INTRODUCTION:

The most uncommon condition is ribose 5 phosphate isomerase (RPI) deficiency, which is brought on by mutations in the enzyme ribose-5-phosphate isomerase, which is involved in the pentose phosphate pathway. Phosphoribosyl pyrophosphate (PRPP) is produced by ribose 5 phosphate, which is initiated via the purine synthesis route. Both the product and the intermediate of the pentose phosphate pathway are ribose and ribose phosphate. The PPP's novel inborn error known as RPI deficiency (i.e. rpi). Deficient conversion of ribulose 5-phosphate to ribose-5-phosphate results in buildup of pentoses and pentose phosphates, which in turn lead to accumulation of ribitol and D-arabitol as metabolic end products. This is the most likely explanation for the biochemical anomalies observed in our patient/patient. Ribose 5 phosphate isomerase has only been diagnosed in three cases in the last 27 years. The world's rarest sickness right now is RPI deficiency. The gene that causes or results in the ribose 5 phosphate isomerase deficiency. Additionally, these are a genetic condition.[1]

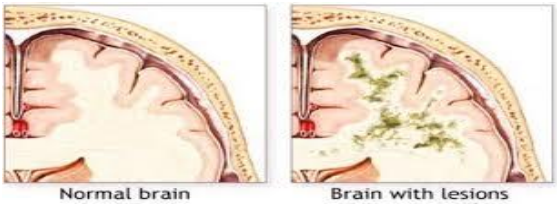
## HISTORY OF RIBOSE 5 PHOSPHATE ISOMERASE DEFICIENCY

A rare disorder called ribose-5-phosphate isomerase deficiency is caused by a mutation in this enzyme. Only one patient with the disease is known to exist; they were diagnosed in 1999. It has been determined that two mutations working together are the cause. Van der Knaap and colleagues discovered the first

case of RPI deficiency in 1999. The boy, then 14 years old, had a frameshift mutation in one allele that caused developmental delay, leukoencephalopathy, seizures, psychomotor retardation, and irregular polyol metabolism. A male born in 1984 to unrelated, healthy parents was the first patient. The patient experienced psychomotor retardation in infancy and began having epilepsy at the age of 4. Beginning at age 7, there was a gradual decline in neurological function, accompanied by notable cerebellar ataxis, mild sensorimotor neuropathy, optic atrophy, and some spasticity. Internal organ organ dysfunction was not observed. D-ribitol and D-arabitol levels were elevated and there were extensive abnormalities of the cerebral white matter in the MRI scans performed at ages 11 and 14.

Upon reviewing the case of the 14-year-old boy in 1999, van der Knaap and associates identified the following symptoms as indicative of RPI deficiency: abnormal polyol metabolism, epilepsy, developmental delay, and subtle psychomotor regression. Subsequently, a second case involving an 18-year-old man with diffuse white matter abnormality, psychomotor regression, and seizures was reported by Naik and colleagues. In 2018, Sklower Brooks and associates reported a third case involving a child who had psychomotor delays and neonatal onset leukoencephalopathy. Kaur and colleagues reported a fourth case in 2019 that included increasing urine polyols (ribitol and arabitol) and progressive leukoencephalopathy

**Fig. no. 01-The Normal Brain and Ribose 5**




**Phosphate Isomerase Deficiency Brain**

**TYPES OF RIBOSE 5 PHOSPHATE ISOMERASE – (RPiA AND RPiB)**

**1. RPiA gene**

The gene for protein coding is called RPIA (ribose 5-Phosphate Isomerase A). A number of illnesses are linked to RPIA, such as glutathione synthetase and ribose 5-phosphate isomerase deficiencies. Using ribose-5-phosphate isomerase A (RpiA), ribose-5-phosphate and ribulose-5-phosphate can be interconverted. Also referred to as RPIA, ribose-5-phosphate isomerase A is an enzyme that is essential to the pentose phosphate pathway (PPP), a metabolic pathway that produces ribose-5-phosphate, which is used in nucleotide synthesis, and NADPH (reduced nicotinamide adenine dinucleotide phosphate).

RPIA is the enzyme that catalyzes the conversion of ribulose-5-phosphate to ribose-5-phosphate. This is a crucial stage in the pentose phosphate pathway's non-oxidative phase, which is in charge of different sugar phosphates' interconversion.

Entire Nucleotide Synthesis Process: The result of RPIA's activity is ribose-5-phosphate, which is a building block for the synthesis of nucleotides, such as DNA and RNA. RPIA is therefore crucial for cell division and growth.

**2. RPiB gene**

The pentose phosphate pathway is a metabolic pathway that produces ribose-5-phosphate, a vital component for nucleotide biosynthesis and other cellular functions. Ribose-5-phosphate isomerase B (RpiB) is an enzyme involved in this pathway. Particularly, ribulose-5-phosphate (R5P) and ribose-5-phosphate (Ru5P) interconversion is catalyzed by RpiB. An essential component for the synthesis of DNA and RNA is ribose-5-phosphate. The activity of RpiB guarantees that nucleotide biosynthesis has access to a sufficient amount of ribose-5-phosphate. An essential component for the synthesis of DNA and RNA is ribose-5-phosphate. The activity of RpiB guarantees that nucleotide biosynthesis has access to a sufficient amount of ribose-5-phosphate. Since nucleotides are the fundamental units of genetic material, RpiB is an essential enzyme for the division and proliferation of cells. Numerous organisms, including bacteria and plants, contain RpiB, whose activity is essential for preserving the nucleotide pools within cells. The enzyme is essential for maintaining equilibrium between the synthesis of ribose-5-phosphate and other cellular metabolic processes.

**Application of the Ribose-5-Phosphate**

1) RPI is a key enzyme in a pentose phosphate pathway.
2) Ribose 5 phosphate is a precursor for the synthesis of Neucleotide and RNA and DNA.

3) The ribose 5 phosphate is key intermediate in the synthesis of pentose sugar which are important for various cellular processes.
4) They also useful in a glycolysis and gluconeogenesis which are central metabolic pathway to regulate glucose metabolism in cells.
5) They useful in biotechnology and biofuel production.
6) They are also used to diagnosing and monitoring various disease.

**Mechanism of ribose 5 phosphate isomerase- (Pentose Phosphate Pathway)**

Ribose 5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH) are the products of the pentose phosphate pathway (PPP), a glucose-oxidizing pathway that proceeds concurrently with upper glycolysis. In the cytoplasm of the cell, the pentose phosphate pathway is active. A) the oxidative phase and B) the non-oxidative phase make up these stages.

**A) Oxidative phase:** Concomitant production of NADPH and the conversion of glucose-6-phosphate to ribulose-5-phosphate characterize this phase.

**B) Non-oxidative Phase:** This stage is in charge of the interconversion of different sugar phosphates, such as ribose-5-phosphate and ribulose-5-phosphate, as well as other sugars.

- **Significance of PPP**

Red blood cells, adipose tissue, and the liver are examples of tissues with high biosynthetic demands, where the PPP is especially significant. Additionally, it is essential for the synthesis of fatty acids and the production of NADPH in the defenses against oxidative damage.

- **Application of PPP**

Knowing the PPP is important for a number of industries, including biotechnology, biomedicine, and the production of biofuels, since it is a vital pathway for the synthesis of NADPH, which is needed for these and other bioprocesses. Cellular redox balance is crucially maintained by the PPP, an essential metabolic pathway that contributes to the energy and biosynthetic needs of cells.

**Ribose 5 Phosphate Isomerase**

A rare genetic condition known as ribose-5-phosphate isomerase deficiency affects the pentose phosphate pathway, which provides ribose-5-phosphate—a necessary molecule for the synthesis of DNA and RNA—by stimulating the pathway. Intellectual disability, seizures, and developmental delay are just a few of the symptoms that this condition can cause. In the pentose phosphate pathway, an enzyme called ribose-5-phosphate isomerase (Rpi) catalyzes the change from ribulose-5-phosphate to ribose-5-phosphate. In the interconversion of different sugar phosphates, this enzyme is essential. A sequence of interactions between the substrate and the enzyme, as well as chemical reactions, are involved in how Rpi catalyzes this reaction.

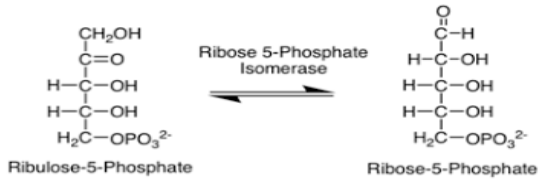



**Fig. no. 02- Conversion of ribulose-5-phosphate to ribose-5-phosphate**

**The conversion can be summarized as follows:**

1) When Rpi is present, ribulose-5-phosphate goes through an isomerization reaction.

2) A carbonyl group shift occurs during the reaction, converting a ketose (ribulose-5-phosphate) into an aldose (ribose-5-phosphate). This enzyme's unique mechanism is based on the creation of an enzyme-substrate complex and the utilization of catalytic residues in the enzyme's active site to speed up the isomerization process. The pentose phosphate pathway is used to prepare the ribose 5 phosphate isomerase. This process yields a variety of materials, including coenzymes, DNA, RNA, and nucleotides.

- **Symptoms of Ribose 5 Phosphate isomerase-**
  - Optic Atrophy
  - Nystagmus
  - Cerebellar Ataxia
  - Seizures
  - Spasticity
  - Leukoencephalopathy (Brain White Matter Disease)
  - Global Developmental Delay

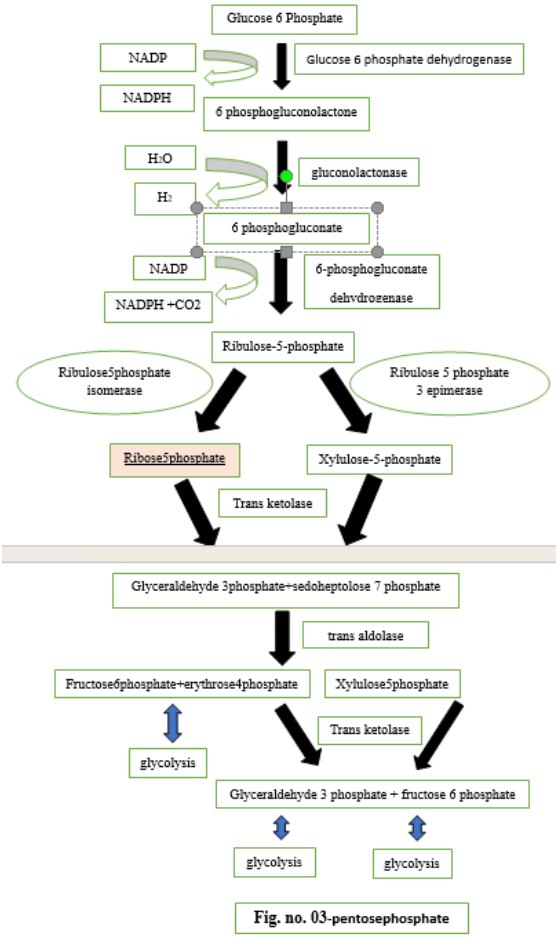



**Fig. no. 03-pentosephosphate**

Those who suffer from leukoencephalopathy in the current generation have defects in the Pentose Phosphate Pathway (PPP), or RPI Deficiency, as well as highly elevated levels of ribitol and D-arabitol in their body fluid and brain. In contrast, a recent report revealed that the patient had abnormal polyol levels in her bodily fluids, a deficiency in transaldolase, and other defects in the pentose phosphate pathway (PPP).

**Diagnosis of ribose 5 phosphate isomerase deficiency**

The diagnosis of these disorder is done without the following symptoms-
1)Developmental Delay
2)Epilepsy
3)Psychomotor Regression
4)Leukoencephalopathy
5)Abnormal Polyol metabolism
6)Seizures
7)Cerebellar Ataxia

**TREATMENT:**

There is no current specific treatment for RPI deficiency. But the symptoms of RPID can be managed by following ways:

**OPTIC ATROPHY:**

A medical condition called optic atrophy is defined by the degeneration or damage of the optic nerve, which can result in either a partial or total loss of vision. Numerous underlying diseases, including multiple sclerosis, trauma, glaucoma, and genetic factors, may be the cause. Depending on the underlying cause, treatment options may involve managing the primary condition or utilizing low-vision aids to enhance the quality of life for the affected individuals.

**CAUSES**

Nerve fibres that transmit impulses to your brain make up your optic nerve. In the case of optic atrophy, something is interfering with your optic nerve's ability to transmit these impulses. Many factors can cause this interference, including:

i. **Lack of proper blood flow (vascular/ischemia):** This is the most common cause of optic nerve atrophy.

ii. **Conditions that you're born with or inherit (congenital):** One condition, Leber's hereditary optic neuropathy, causes you to lose vision in one eye first and then the other.

iii. **Damage from inflammation, either from other diseases or swelling in the optic nerve itself:** One cause is optic neuritis, which is inflammation of your optic nerve. Another is hydrocephalus, or fluid collection in your brain.

iv. **Damage from diseases of the retina:** Retinal diseases include diabetes-related retinopathy and retinal vein occlusion.

**SYMPTOMS**

Optic atrophy symptoms relate to changes in vision, including:

i. Blurred vision or a reduction in sharpness of vision.
ii. Difficulties with peripheral vision.
iii. Difficulties with colour vision.

**CEREBELLAR ATAXIA:**

A neurological condition known as cerebellar ataxia affects the cerebellum, which is in charge of coordinating voluntary muscle movements, balance, and posture. Cerebral ataxia is a condition characterized by difficulties with balance and walking, slurred speech, and muscle weakness. It can be caused by genetic mutation, acquired conditions such as stroke, tumor, or multiple sclerosis, and alcohol abuse. They suffer from both hereditary and non-genetic forms of cerebral ataxia, as well as uncoordinated movement brought on by a cerebellar lesion. The medication ACETAZOLAMIDE can be used to treat episodic ataxia, and lifestyle changes can also be recommended. Antibiotics and antivirals can be used to treat acquired ataxia. (12,13)

**CAUSES**

Damage to the part of your brain that controls muscle coordination (cerebellum) or its connections can cause ataxia.

i. **Alcohol.** Long-term excess alcohol intake may cause persistent ataxia. It's possible it may improve by avoiding alcohol completely.
ii. **Medications.** Ataxia is a potential side effect of certain medications, especially barbiturates, such as phenobarbital; sedatives, such as benzodiazepines; antiepileptic drugs, such as phenytoin; and some types of chemotherapy.
iii. **Thyroid problems.** Hypothyroidism and hypoparathyroidism can cause ataxia.
iv. **COVID-19 infection**. Ataxia most commonly results from severe COVID-19 cases.
v. **Hereditary causes**:Some types of ataxia and some conditions that cause ataxia are hereditary.

**SYMPTOMS**

Ataxia can develop over time or come on suddenly. Ataxia is a sign of several neurological disorders and can cause:

i. Poor coordination
ii. Walking unsteadily or with the feet set wide apart
iii. Poor balance
iv. Difficulty with fine motor tasks, such as eating, writing or buttoning a shirt
v. Involuntary back-and-forth eye movements (nystagmus)
vi. Difficulty swallowing

**(Fig. no. 04) Cerebellar Ataxia**

**SEIZURES:**

MRI, CT, CAT, and EEG scans are among the tests that recommend an early diagnosis. Anti-epileptic medications and weight loss are part of the treatment. Uncontrollably abrupt electrical disruptions in the brain that can result in a variety of symptoms are known as seizures. Usually, they fall into one of two categories: a) Partial seizures; b) Generalized seizures. (5,6)

**CAUSES**

Seizures can have various causes, including:

i. **Epilepsy:** A neurological disorder where recurrent seizures occur without an identifiable trigger.
ii. **Brain injury:** Traumatic brain injury, stroke, or brain tumors can lead to seizures.
iii. **Metabolic disorders:** Imbalances in blood sugar, electrolytes, or other metabolic factors can trigger seizures.
iv. **Genetics**: Some individuals have a genetic predisposition to seizures.
v. **Fevers**: High fevers, especially in children, can cause febrile seizures.
vi. **Brain abnormalities:** Structural issues in the brain, such as malformations or lesions, can lead to seizures.

**SYMPTOMS**

Seizures symptoms vary and can include,

i. Sudden Change In Awareness Or Full Loss Of Consciousness.
ii. Involuntary Twitching Or Stiffness In The Body Or Severe Stiffening.
iii. Limb Shaking With Loss Of Consciousness (A Convulsion.)

**SPASTICITY:**

Daily stretching exercises help to improve motor flexibility and can help to decrease it. A medical condition called spasticity is characterized by stiffness or elevated muscle tone. It is frequently linked to diseases like multiple sclerosis, stroke, cerebral palsy, and spinal cord injuries. Damage to the central nervous system is the cause of them. Anti-spasticity and muscle relaxant medications can lessen the likelihood of spasticity. Another treatment option for spasticity is a change in lifestyle that includes a balanced diet and frequent exercise. (11)

**CAUSES**

Spasticity is a condition characterized by muscle stiffness and involuntary muscle contractions. It can be caused by various factors, including:

**Neurological Disorders:** Spasticity is often associated with neurological conditions such as multiple sclerosis, cerebral palsy, stroke, and spinal cord injury. These conditions can disrupt the normal communication between the brain and muscles, leading to spasticity.

**Brain and Spinal Cord Injuries**: Traumatic injuries to the brain or spinal cord can damage the nerve pathways that control muscle function, resulting in spasticity.

**Stroke**: When a stroke occurs, it can damage specific areas of the brain, leading to spasticity as a potential complication.

**Multiple Sclerosis**: This autoimmune disease affects the central nervous system and can result in spasticity due to the damage to nerve fibers.

**Cerebral Palsy**: Spasticity is a common symptom in individuals with cerebral palsy, a condition that affects movement and muscle coordination from an early age.

**SYMPTOMS:** Symptoms of spasticity can vary from being mild stiffness or tightening of muscles to painful and uncontrollable spasms. Pain or tightness in joints is also common in spasticity.

i. Muscle stiffness, causing movements to be less precise and making certain tasks difficult to perform.
ii. Muscle spasms, causing uncontrollable and often painful muscle contractions.
iii. Involuntary crossing of the legs.
iv. Muscle and joint deformities.

**LEUKOENCEPHALOPATHY**:

A class of diseases known as leukoencephalopathy mainly affect the brain's white matter. staying away from medications that affect the immune system. Leukoencephalopathies come in a variety of forms and can be brought on by a number of things, such as genetic mutations, infections, toxins, or underlying medical conditions. Typical leukoencephalopathies include.(7,8)

1)Metachromatic leukodystrophy
2)Adrenoleukodystrophy (ALD)
3)Multiple sclerosis (MS)
4)Progressive multifocal leukoencephalopathy (PML)
5)Canavan disease

**CAUSES**

**Genetic Mutations:** Some forms of leukoencephalopathy are caused by genetic mutations that affect the development and maintenance of the white matter in the brain. Examples include X-linked leukoencephalopathy and leukodystrophies.

**Metabolic Disorders:** Certain metabolic disorders can lead to the accumulation of toxic substances in the brain, damaging the white matter. Conditions like Canavan disease and adrenoleukodystrophy fall into this category.

**Infections**: Infections of the central nervous system, such as progressive multifocal leukoencephalopathy (PML), can lead to leukoencephalopathy.

**Autoimmune Disorders**: Conditions like multiple sclerosis (MS) involve an autoimmune attack on the

white matter of the brain, resulting in demyelination and leukoencephalopathy.

**Toxic Exposure:** Exposure to toxic substances like certain drugs, solvents, or heavy metals can damage the white matter and result in leukoencephalopathy.

**SYMPTOMS**

Symptoms may include any of the following:

i. Loss of coordination, clumsiness.
ii. Loss of language ability (aphasia)
iii. Memory loss.
iv. Vision problems.
v. Weakness of the legs and arms that gets worse.

**NYSTAGMUS:**

The medical condition known as nystagmus is characterized by rapid, repetitive, and involuntary eye movements. These eye movements can be rotary, up and down (vertical), or side to side (horizontal). Nystagmus may develop later in life or be congenital, meaning it is present from birth. It could have a number of underlying causes, such as inner ear issues, neurological conditions, or specific drugs. Nystagmus can impair balance and coordination in addition to reducing vision. Depending on the underlying cause, there may be several treatment options available, such as treating the core problem or corrective lenses to enhance vision. To determine the cause of the action, routine eye exams are advised.(9,10)

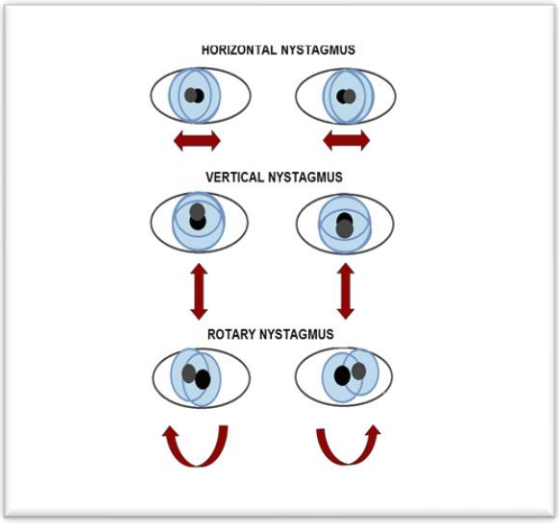



**Fig. no 05-Nystagmus**

**CAUSES**

Nystagmus is an involuntary, rhythmic eye movement. It can have various causes, including:

i. **Inner ear problems (vestibular nystagmus):** Often related to issues with the inner ear's balance system, such as benign paroxysmal positional vertigo (BPPV) or Meniere's disease.
ii. **Vision problems (optokinetic nystagmus):** Occurs when the eyes attempt to track a moving object but can't keep up, as in reading while moving in a car.
iii. **Neurological conditions:** Nystagmus can be a symptom of neurological disorders like multiple sclerosis or brainstem lesions.
iv. **Medications or drugs:** Certain medications or substances can cause nystagmus as a side effect.

**SYMPTOMS**

i. Involuntary eye movement, often side-to-side or up-and-down.
ii. Reduced vision, especially when the eyes are not stable.
iii. Dizziness or vertigo, which can be triggered by the eye movements.
iv. Oscillopsia, a perception that stationary objects are moving.

**EPILEPSY**

The neurological condition known as epilepsy is typified by recurrent seizures, which are abrupt, uncontrollable electrical disruptions in the brain. Since epilepsy is a chronic illness, managing it may require making lifestyle adjustments such as getting enough sleep, controlling stress, and avoiding triggers. The length and severity of these seizures can vary. Brain traumas, infections, and genetic factors can all contribute to epilepsy.

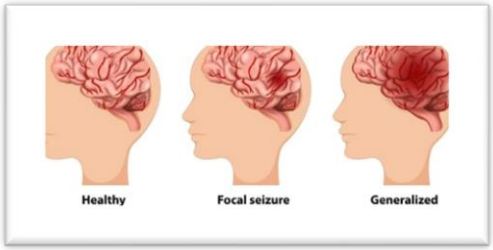
They can be diagnosed using imaging studies like MRIs and CT scans, medical histories, and ECG tests. A person's ability to drive, work, and engage in certain activities can all be impacted by epilepsy. For this reason, having a strong support network and medical professionals on hand can be extremely beneficial.(5,6)

**CAUSES**

i. **Idiopathic:** In many cases, the exact cause is unknown, and this is referred to as idiopathic epilepsy. It often has a genetic basis.
ii. **Symptomatic:** Epilepsy can be a symptom of an underlying condition or injury, such as brain tumors, head injuries, strokes, or infections like encephalitis or meningitis.
iii. **Genetic:** Some forms of epilepsy have a strong genetic component and can be passed down through families.
iv. **Structural:** Abnormalities in the structure of the brain, such as malformations or developmental disorders, can lead to epilepsy.
v. **Metabolic:** Imbalances in the body's chemical processes can trigger seizures. These metabolic disorders are relatively rare but can lead to epilepsy.
vi. **Febrile:** Febrile seizures occur in young children during a high fever. While they are usually harmless, they can be a precursor to epilepsy in some cases.

**SYMPTOMS-**

i. Musal Contaction
ii. Loss Of Conciousnes
iii. Anxiety
iv. Staring
v. Weakness




**(Fig. no. 06) Epilepsy**

**CONCLUSION**

An innovative inborn error in the PPP is RPI deficiency. The most likely explanation for our patient's biochemical abnormalities is that pentoses and pentose phosphates accumulate due to insufficient conversion of ribulose 5-phosphate into ribose-5-phosphate, which in turn accumulates ribitol and darabitol as metabolic end products. Mutations in the enzyme ribose-5-phosphate isomerase, which is involved in the pentose phosphate pathway, result in ribose-5-phosphate isomerase deficiency, or RPI deficiency, a disorder that affects people. A rare genetic condition known as ribose-5-phosphate isomerase deficiency affects the pentose phosphate pathway, resulting in a shortage of the enzyme ribose-5-phosphate isomerase. Numerous symptoms, such as anemia, developmental delays, and other health problems, may arise from this.In conclusion, for people with this condition to enhance their quality of life and manage the related health challenges, early diagnosis and appropriate medical management are essential. Because of this combination, it was discovered that different tissues and cell types had different RPI activity. Higher levels of ribitol and arabitol in a metabolic profile, along with variations in polyol profiles, are features of the RPI deficiency. Other symptoms include leukoencephalopathy and neuropathy, which could be brought on by an excess of ribitol and arabitol or possibly by a deficiency of ribose-5-phosphate during the synthesis of RNA.A pentose phosphate pathway enzymopathy is ribose 5-phosphate isomerase (RPI) deficiency. It is one of the rarest human disorders, with only one diagnosed case, and presents with progressive leukoencephalopathy and peripheral neuropathy.

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