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Review

A Metabolism Perspective on Pediatric Rhabdomyolysis

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ABSTRACT

Rhabdomyolysis is a clinical emergency that can result in life-threatening complications. The etiology for rhabdomyolysis is broad. Infecitons are the most common cause in pediatric patients. Underlying inherited metabolic diseases are also a cause of rhabdomyolysis and can often have a diagnostic challenge, considering their marked heterogeneity and comparative rarity. The purpose of this review is to summarize the essential characteristics and diagnostic clues of inborn errors of metabolism associated with rhabdomyolysis.

Keywords: Rhabdomyolysis, inborn errors of metabolism, diagnosis

INTRODUCTION

Rhabdomyolysis is a clinical condition resulting from skeletal muscle fibers damage due to many reasons. The damaged muscle cell breaks down, and the intracytoplasmic proteins such as creatine kinase (CK) and myoglobin are released into the plasma. Subsequently, it can cause life-threatening complications such as electrolyte disturbance, acute kidney injury (AKI), and disseminated intravascular coagulation. These causes include severe trauma, vigorous exercise, burns, electrical injury, prolonged immobilization, seizure, electrolyte imbalances such as hypokalemia, hyponatremia, hypophosphatemia, and drugs such as levetiracetam, colchicine, lithium, and infectious agents such as Mycoplasma pneumoniae, enteroviruses, Human parainfluenza viruses (Table 1).[1,2]

Although there is a lack of consensus for diagnosis, in the pediatric literature, CK level greater than five times the upper limit of normal, or greater than 1.000 U/L, is commonly used for diagnosis. Myalgia, weakness, and red urine are common complaints with elevated CK. This differs from myositis, in which there is muscle inflammation. However, the cell wall remains intact, so minimal intracellular content leaks into the circulation, and the serum CK level is much lower than 1.000 U/L.[1-3]

If rhabdomyolysis is suspected, the physician can confirm the diagnosis by detecting elevated serum CK levels. Rhabdomyolysis is a cause of red urine (Table 2). In the absence of red blood cells in the sediment, Heme-positive urine should raise the suspicion for hemolysis or rhabdomyolysis. Detecting urine myoglobin can be helpful for the diagnosis of rhabdomyolysis.[4,5] Early recognition of rhabdomyolysis by pediatricians is vital because it can be encountered oftenly in the pediatric routine due to various etiologies and is mortal when there is delay in treatment.[6]

Inborn errors of metabolism (IEM) are also one of the main topics in the etiology of rhabdomyolysis. These conditions are listed in Table 3. IEMs may be overlooked, considering the high frequency of viral infections in pediatrics and the fact that these infections are the most common causes of rhabdomyolysis. Pediatricians should consider IEMs when symptoms are recurrent, progressive, unexplained, unresponsive to standard treatment, or inexplicably associated with the involvement of other organ systems. Consanguinity and patients who have similar clinical features in

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family history are other supportive findings.[3,7] This review aims to provide pediatricians with an overview of IEMs that can present with rhabdomyolysis. A summary of these conditions with a focus on diagnostic tools is presented in Figure 1.[8]

Glycogen Storage Diseases

Glycogen storage diseases (GSDs) are inherited carbohydrate metabolism errors and are classified into two groups as hepatic and muscle glycogenoses. Hepatomegaly, hypoglycemia, elevated transaminases, and hepatosteatosis are common findings in hepatic glycogenosis. Glycogen is an important energy source for skeletal muscle during exercise. The absence of enzymes involved in glycogenolysis causes defective glycogen breakdown and results in exercise intolerance, muscle cramps, and rhabdomyolysis in muscle glycogenosis. If the absent enzyme is also en enzyme expressed in tissues other than liver and skeletal muscle, other clinical manifestations such as neutropenia, hemolytic anemia, or proximal tubular dysfunction may occur depending on the affected tissue. The first diagnostic tool is, if available, a demonstration of glycogen storage and enzyme deficiency in the liver or muscle. Molecular analyses confirm the diagnosis.[9,10]

GSD type V (Myophosphorylase deficiency, McArdle disease)

The GSD type V is the most common and well-known type of muscle glycogenosis. GSD type V is also known as McArdle disease. Myophosphorylase deficiency results in defective glycogenolysis in skeletal muscle. Typical symptoms are exercise intolerance with myalgia and stiffness of exercising muscles, which are relieved by rest. This clinical issue is named "second wind phenomenon". Two types of effort are more responsible for symptoms: brief, intense isometric exercise, such as lifting heavy weights, or constant

Table 1. Causes of pediatric rhabdomyolysis

Infections	Mycoplasma pneumoniae
	Primary (acute) q fever
	Enterovirus
	Human parainfluenza viruses
	West Nile encephalitis
	Inflammatory bowel disease
	Bacillus cereus
	COVID-19
Fluid and electrolyte imbalances	Water intoxication
	Hypokalemia
	Hyponatremia
	Hypophosphatemia
Muscle strain/excessive activity/trauma	Burns
	Prolonged immobilization
	Electrical injury
	Blunt trauma and crush injuries
Medications	Propofol
	Cholesterol-lowering drugs
	Levetiracetam
	Daptomycin
	Colchicine
	Lithium
	Synthetic marijuana
Inherited neuromuscular disorders	Malignant hyperthermia-susceptibility
	Anoctaminopathy-5
	Duchenne muscular dystrophy
	Becker muscular dystrophy
	Limb-girdle muscular dystrophy (2B and 2I)
	Marinesco-Sjogren syndrome
	Pontocerebellar hypoplasia type 2
Inborn errors of metabolism	(see Table 3)

COVID-19: Coronavirus disease-2019

Table 2. Causes of red urine without RBCs

Heme positive	
Hemoglobinuria	Hemolytic anemias
	Hemolytic-uremic syndrome
	Cystitis
Myoglobinuria	Rhabdomyolysis
Heme negative	
Drugs	Adriamycin
	Chloroquine
	Deferoxamine
	Hydroxycobalamin
	Ibuprofen
	Iron sorbitol
	Levodopa
	Metronidazole
	Nitrofurantoin
	Phenytoin
	Quinine
	Rifampin
	Salicylates
	Sulfasalazine
Foods	Beets
	Blackberries
	Paprika
	Red food coloring
Porphyrinuria	Disorders of "Heme" metabolism

RBCs: Red blood cells

dynamic exercise, such as running fastly or climbing uphill.[9,11] Clinical examination is usually normal between rhabdomyolysis episodes, but a proximal muscle or scapulohumeral weakness and wasting may occur in the fourth decade of life. Baseline CK levels are high, and CK can increase to more than 100,000-1,000.000 UI/L during episodes of rhabdomyolysis, causing a risk of developing AKI. Myoglobinuria occurs in about half of the patients. The ischaemic forearm exercise test (IFET) was first used as a diagnostic tool. The abnormal increase in ammonia and the absence of lactate elevation during exercise support GSD-V diagnosis. Due to the risk of rhabdomyolysis, the standardized non-ischaemic FET has replaced the ischaemic test. Muscle biopsy shows storage and negative myophosphorylase staining. Muscle biopsy should be performed several weeks after a rhabdomyolysis episode. Recently, muscle biopsy may be avoided if sequencing of *PYGM* gene is available.[10]

Table 3. Inborn errors of metabolism to consider in rhabdomyolysis

Glycogen storage diseases	GSD type V
	GSD type Ixd
Disorders of glycolysis	ALDOA deficiency
	LDH deficiency
	Muscle phosphofructokinase deficiency
	PGK deficiency
Disorders of mitochondrial fatty acid oxidation	Carnitine transporter deficiency
	Carnitine palmitoyltransferase II deficiency
	VLCAD deficiency
Mitochondrial disorders OXPHOS deficiencies	
Others	Lipin-1 deficiency
	TANGO2

ALDOA: Aldolase A, GSD: Glycogen storage disease, LDH: Lactate dehydrogenase, PGK: Phosphoglycerate kinase, VLCAD: Very long-chain acyl-CoA dehydrogenase, OXPHOS: Oxidative phosphorylation system, TANGO2: Transport and Golgi organization 2

There is no grateful therapy for GSD-V. Oral sucrose, ribose, or glucose ingestion together with abundant hydration before exercise is recommended to prevent rhabdomyolysis.[12,13] Recently, a pilot study showed that a modified ketogenic diet might improve symptoms and exercise tolerance in patients with GSD-V.[12]

GSD type IXd (Muscle phosphorylase kinase deficiency)

GSD type IXd is caused by muscle phosphorylase kinase deficiency. Muscle phosphorylase kinase deficiency is an X-linked disorder caused by mutations in PHKA1, which encodes the α1 subunit. GSD-IXd is a cause of cramps, exercise intolerance and raised CK. The second wind phenomenon occurs. These symptoms are similar to GSD-V. They are usually milder and present anytime from childhood to adulthood. Rhabdomyolysis has been reported in patients with GSD-IXd. There is a variable lactate response with the non-ischaemic FET. Symptoms should be managed as in other muscle glycogenosis.[10,13,14]

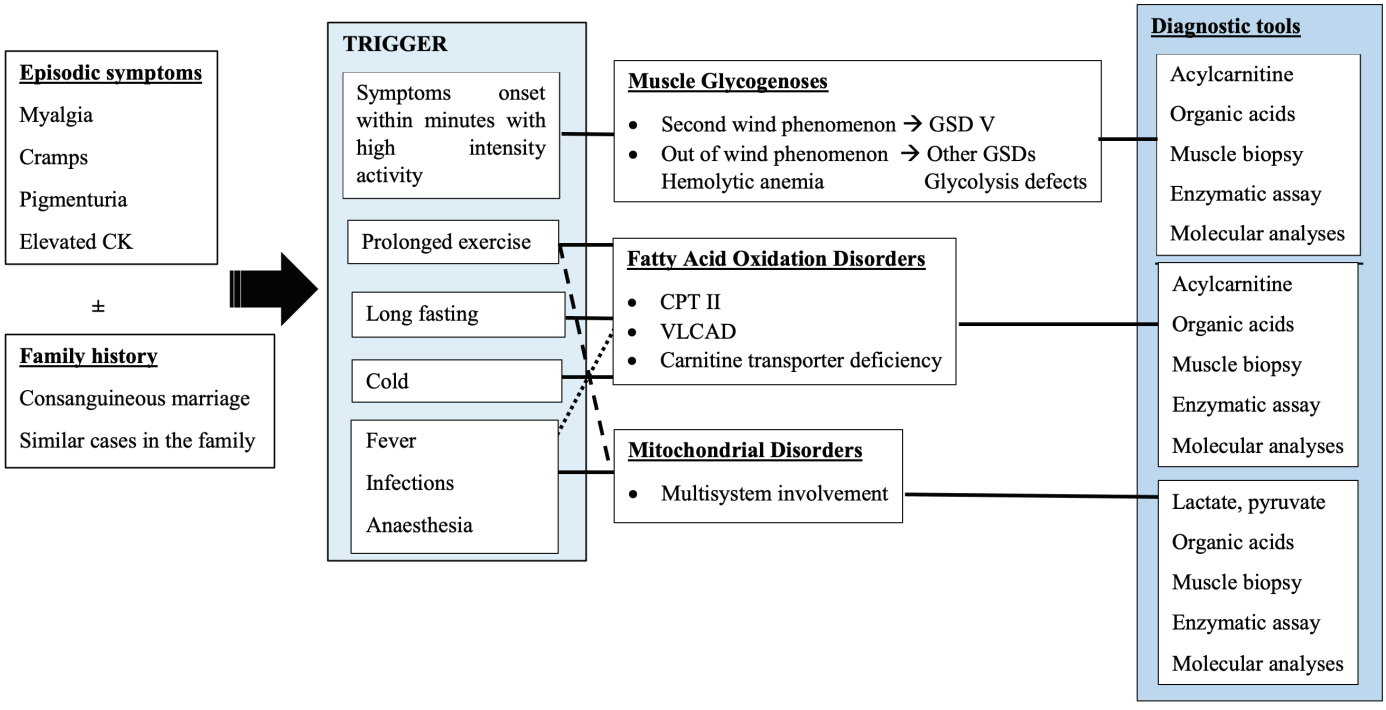

Figure 1. Algorithm for metabolic etiologies of rhabdomyolysis

CK: Creatine kinase, GSD: Glycogen storage disease, CPT: Carnitine palmitoyltransferase, VLCAD: Very long-chain acyl-CoA dehydrogenase

Disorders of Glycolysis

ALDOA deficiency (GSD type XII)

Aldolase catalyzes the reversible conversion of fructose-1,6-bisphosphate to glyceraldehyde 3-phosphate in glycolysis. Aldolase A (ALDOA) is a predominant isoform of aldolase in skeletal muscle and erythrocytes. Single cases with very variable symptoms are reported very rarely. The main clinical findings are hemolytic anemia, recurrent episodes of rhabdomyolysis, usually precipitated by fever, and mental retardation. CK levels are normal or elevated at rest. Muscle biopsy usually reveals non-specific alterations and biochemical studies performed in muscle or erythrocytes show diminished ALDOA activity.[15]

There is no specific treatment. Avoiding vigorous exercise that may cause rhabdomyolysis is the main principle of management.[16]

LDH deficiency (GSD type XI)

Lactate dehydrogenase (LDH) has two subunits, namely muscle (M) and heart (H). There are five isoenzymes (LDH1-5) consisting of these two subunits. *LDHA* and *LDHB* genes encode the M and H proteins, respectively. LDHA mutations result in the deficiency of the LDH and they are very rare. It mainly affects skeletal muscles because skeletal LDH has all M-subunits.[17] In addition to muscle symptoms, a few affected patients suffered from skin rashes.[16,18] In patients with myoglobinuria, LDH deficiency should be kept in mind in the presence of low LDH despite elevated CK.[16]

Muscle phosphofructokinase deficiency (GSD type VII, Tarui disease)

There are three isoforms of phosphofructokinase; muscle, liver, and platelet isoforms. Muscle phosphofructokinase has the main role in glycolysis and the conversion of fructose 6-phosphate to fructose 1,6-bisphosphate. In GSD-VII, there is blockage of glycolysis resulting from a deficiency of the enzyme muscle phosphofructokinase due to mutations in the *PFKM* gene. The main clinical symptom is exercise intolerance, same as in GSD-V. The onset of classic form is usually in childhood. The main clinical features are muscle cramps, exercise intolerance, rhabdomyolysis, and myoglobinuria, often associated with hemolytic anemia and hyperuricemia but without the second wind phenomenon. Patients with late-onset form suffer from myalgia later in life. Infantile onset form may present as floppy infants. Infantile onset patients have no hemolytic anemia.[11,16]

The CK at rest is typically raised in GSD-V but may be normal in GSD-VII. A flat lactate curve, a normal increase of ammonia in non-ischaemic FET, and increased bilirubin and reticulocyte counts are helpful for differentiation from GSD-V. Biochemical assay of the muscle phosphofructokinase level and *PFKM* gene analysis are required for diagnosis.[11,16]

No specific treatment exists. The patients should avoid a high carbohydrate diet and strenuous exercise, as glucose cannot be metabolized. According to a recent, 5-year follow-up study, ketogenic diet can benefit.[19]

Muscle Phosphoglycerate Kinase Deficiency

Phosphoglycerate kinase (PGK) deficiency is a rare X-linked metabolic disorder caused by mutations in the *PGK1* gene. There are three main clinical presentations; non-spherocytic hemolytic anemia, myopathy, or the combination of anemia and central nervous system involvement. The myopathic form is indistinguishable from PFK deficiency and is characterized by recurrent episodes of exercise-induced cramps and myoglobinuria. The onset is usually in childhood.

Definitive diagnosis requires a biochemical assay of the PGK enzyme activity in muscle and/or erythrocytes and *PGK1* gene analysis.[20]

No specific treatment or cure exists. Management primarily consists of avoiding strenuous exercise. Symptoms typically resolve with rest.[16]

Disorders of Mitochondrial Fatty Acid Oxidation

Carnitine transporter deficiency

Carnitine transporter deficiency, also called systemic carnitine deficiency, is caused by a lack of the sodium-dependent carnitine transporter protein OCTN2. Carnitine cannot pass through the plasma membrane. Therefore, entry of Acyl-CoA esters, transported by binding to carnitine, into the mitochondrial fatty acid oxidation cycle is disrupted. Carnitine which cannot be transported into the cell is lost through the kidneys, and plasma and intracellular carnitine levels decrease. For plasma, carnitine levels of patients are <5 μM/L, while the normal range is 25-50 μM/L. The most fundamental clinical features are progressive cardiomyopathy and myopathy. Hypoglycemia and encephalopathy attacks may occur. It can cause sudden infant death. Older children have rhabdomyolysis, even in the absence of myopathy and cardiomyopathy. Asymptomatic or mild patients diagnosed by using neonatal screening were reported.Plasma carnitine level is tried to be kept above 10 μM/L with high-dose carnitine support (100-300 mg/kg/day). Response to treatment is good.[21,22]

Carnitine palmitoyltransferase II deficiency

Long-chain fatty acids do not cross the bilayer mitochondrial membrane. Thus, carnitine palmitoyltransferase (CPT) I and II afford long-chain fatty acids transport into the mitochondrial compartment. CPT II protein is in the inner mitochondrial membrane. CPT II deficiency is an autosomal recessive disorder of long-chain fatty acid oxidation.

There are three clinical phenotypes in CPT II deficiency; lethal neonatal form, severe infantile hepatocardiomuscular form, and myopathic form.[23] Lethal neonatal form manifests with hypoketotic hypoglycemia, liver failure, cardiomyopathy, respiratory distress, and/or cardiac arrhythmias. Liver and brain calcifications, cystic dysplastic kidneys, and neuronal migration defects have been reported.[24,25] Severe infantile hepatocardiomuscular form presents with hypoketotic hypoglycemia, liver failure, cardiomyopathy, and peripheral myopathy.[25,26]

The myopathic form is usually mild and can manifest from infancy to adulthood. The unbalanced sex distribution was reported in previous studies. More than 75% of patients reported were male thus far.[27] It is clinically characterized by recurrent episodes of muscle pain, muscle weakness, and rhabdomyolysis. These episodes are triggered mainly through exercise, prolonged fasting, exposure to cold, fever, infection, menstruation, emotional stress. Affected individuals generally do not have muscle weakness in between the attacks. Renal failure requiring hemodialysis due to acute tubular necrosis is also occasionally reported during rhabdomyolysis attacks. The overall increase of C12 to C18 acylcarnitines will support the diagnosis of CPT II deficiency. The increases in C16+C18: 1 and (C16+C18:1)/C2 ratios are more specific than other acylcarnitine measurements. The absence of the typical acylcarnitine profile does not exclude the diagnosis of CPT II deficiency, especially the mild myopathic form.[28,29] Decreased CPT II activity and histopathological changes consisting lipid accumulation can be detected in muscle biopsy. Previous reports showed that muscle biopsies might be normal and showed non-specific changes or lipid deposition.[30] The diagnosis should be confirmed by *CPT II* gene analysis.[23] CPT II deficient patients should avoid prolonged fasting and excessive muscle exercise in long-term treatment. Dietary therapy should be suggested to provide energy based on fractionated meals rich in carbohydrates and medium-chain triglyceride (MCT).[31]

Very long-chain acyl-CoA dehydrogenase deficiency

Very long-chain acyl-CoA dehydrogenase (VLCAD) plays a role in mitochondrial β-oxidation of long-chain fatty acids. There are three phenotypes reported. The severe or early-onset form typically presents within the first few months of life. It is characterized by hypertrophic or dilated cardiomyopathy and arrhythmias, hypotonia, hepatomegaly, and intermittent hypoglycemia. The moderate form typically presents during late infancy or early childhood with episodes of hypoketotic hypoglycemia and hepatomegaly. Cardiomyopathy is much less likely in moderate than in severe phenotypes. The mild or late-onset form is typically present in adolescence or early adulthood and is characterized by exercise intolerance and rhabdomyolysis. Episodic rhabdomyolysis may be provoked by infection, cold, fasting, exercise, or emotional stress.[22,25] The specific marker for VLCAD from dried blood spots is an elevation of C14:1 acylcarnitine. Other long-chain acylcarnitines and/or abnormal ratios of C14:1 and other acylcarnitines support the diagnosis of VLCAD deficiency. The acylcarnitine profile can be completely normal in patients with mild VLCAD, which should be kept in mind. There is usually dicarboxylic aciduria, especially during severe metabolic decompensation. Muscle biopsy may show lipid storage, and the electromyography is often myopathic. Clinical and acylcarnitine profiles may be confused with CPT II deficiency. Enzyme analysis can be done for diagnosis. Diagnosis needs to be confirmed by enzyme assay of VLCAD or by mutation analysis of *ACADVL* encoding VLCAD.[25]

Prolonged fasting should be avoided in patients in order to prevent acute metabolic decompensation. Frequent, regular feeds which are high carbohydrate-low fat are recommended. For providing a source of energy; MCT, by-passing the enzymatic block in β-oxidation is preferable. A bolus of MCT before exercise can prevent rhabdomyolysis in patients with myopathic VLCAD deficiency.[25,32] Triheptanoin (C7 odd-chain fatty acid) can substitute for MCT in patients with VLCAD deficiency.[33]

Rhabdomyolysis attacks may result in life-threatening events such as acute renal failure requiring hemodialysis. Generally, the treatment of rhabdomyolysis is conservative such as intravascular volume expansion, urinary alkalinization.[34]

Mitochondrial oxidative phosphorylation system disorders

The oxidative phosphorylation system (OXPHOS) is the final step in the aerobic production of adenosine triphosphate. The OXPHOS consists of 5 protein complexes (Complex I-V) and 2 electron carriers embedded in the inner mitochondrial membrane. Defects in OXPHOS can be caused by a mutation in either mitochondrial DNA or nuclear DNA.

Most patients with mitochondrial disorders present with a multisystem disorder at any age, and the symptoms are almost progressive. The most commonly affected organs are the brain, kidney, heart, and skeletal muscle, all of which require the most energy.[35,36]

Mitochondrial myopathies lead to muscle energy failure due to dysfunction of the mitochondrial respiratory chain, coded by both mitochondrial and nuclear genome. It can be a non-progressive disease, but life-threatening episodes of rhabdomyolysis may occur. There is no effective treatment available for mitochondrial myopathies.[37-39]

Others

Muscle phosphatidic acid phosphatase deficiency (Lipin-1 deficiency)

Lipin-1 (LPIN1) is a phosphatidic acid phosphohydrolase that catalyzes the dephosphorylation of phosphatidic acid to diacylglycerol and inorganic phosphate. It regulates critical metabolic pathways, such as adipocyte differentiation and lipid metabolism, nuclear envelope and mitochondrial dynamics, and vacuole fusion. LPIN1 encodes Lipin-1.

LPIN1 deficiency is one of the leading metabolic causes of recurrent rhabdomyolysis episodes in children. Deficiency of this enzyme causes potentially fatal rhabdomyolysis triggered by infection. It should be kept in mind if normal acylcarnitines are detected in patients with recurrent rhabdomyolysis. Despite the known roles of LPIN1 in lipid biosynthesis and transcriptional regulation, the pathogenic mechanisms causing rhabdomyolysis are unclear.

There is no known effective treatment for LPIN1 deficiency. Symptomatic treatment of rhabdomyolysis, high energy intake from carbohydrates, and monitoring for hyperkalemia and cardiac arrhythmias are reported in the management of rhabdomyolysis.[40-42]

TANGO2 Deficiency

The Transport and Golgi Organization protein 2 (TANGO2) protein regulates the organization of the Golgi apparatus and the endoplasmic reticulum. Mutations in TANGO2 have been recently described in episodic rhabdomyolysis. Clinical findings are hypoglycemia, hyperammonemia, and susceptibility to life-threatening cardiac tachyarrhythmias. Neurologic abnormalities, developmental delay, and intellectual disability are other accompanying clinical courses of patients. Other clues for suspicion of TANGO2 deficiency are hypothyroidism, QT prolongation, or abnormalities of long-chain acylcarnitines and urine dicarboxylic acids. TANGO2 deficiency mimics fatty acid oxidation defects, except for ketosis.[43-45]

There is no specific known treatment for TANGO2 deficiency. Treatment of rhabdomyolysis and organic complications (e.g., hyperammonemia, seizures, arrhythmias) is fundamental in managing attacks. Anabolizing management, treatment with vitamin B1, B2, and carnitine were reported to stabilize metabolic decompensation.[46]

CONCLUSION

Pediatricians should consider IEMs in the differential diagnosis of rhabdomyolysis. It should not be forgotten that IEMs have high prevalence due to the high rate of consanguineous marriages in our country. The road to diagnosis starts with the suspicion of the clinician and a thorough clinical evaluation.

Ethics

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