CASE REPORT

Congenital Erythropoietic Porphyria (Gunther Disease)

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ABSTRACT

Porphyria encompasses class of disorders that manifest due to accumulation of porphyrins in body secondary to deficiency of enzymes involved in heme synthetic pathway. Congenital erythropoietic porphyria (CEP) is a very rare type of porphyria that results from deficiency of enzyme uroporphyrinogen III cosynthase (UROS).Painful photosensitivity and erythrodontia are clinical hallmarks of CEP.

This case report is about a 17 months old boy who presented with reddish discoloration of urine, erythrodontia and painful sclerodermatous rash .Diagnosis was mainly made on clinical basis and was confirmed on finding the elevated urinary levels of uroporphyrin and coproporphyrin.He was treated with vitaminD supplements, cimetidine and avoidance of sunlight. The patient improved with treatment but dyspigmentation and scarring of skin were persisting. This case highlights the importance of diagnosing these metabolic disorders as timely intervention can prevent serious consequences.

Key Word: *Porphyria, Uroporphyrin III synthetase, Sclerodermatous rash, Reddish discoloration of urine*

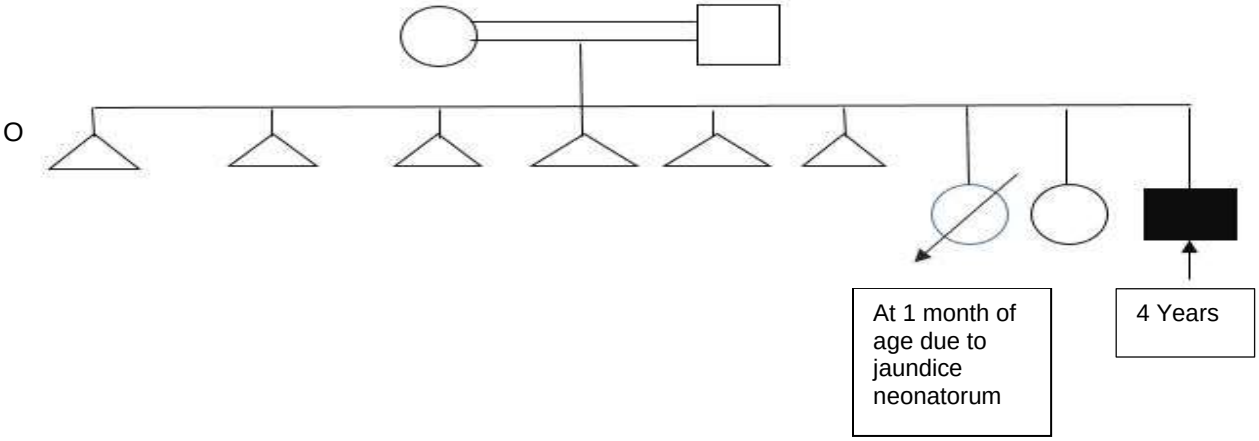
INTRODUCTION

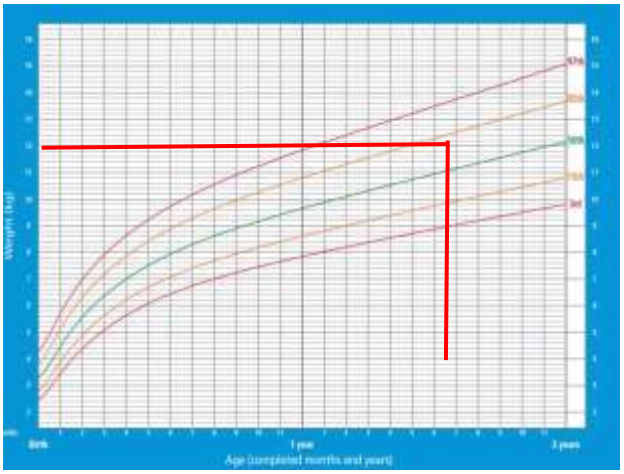
Porphyria consists of spectrum of disorders occurring due to enzymatic defect in biosynthetic pathway of heme which leads to building of toxic precursors of heme porphyrin. There are two main types of porphyrias based on predominant symptoms. Acute porphyrias with neurovisceral symptoms; abdominal pain, neuropathy, psychosis and autonomic disturbance. Acute intermittent porphyria (AIP) is the most common porphyria of this category Congenital erythropoietic porphyria (CEP), Porphyria cutanea tarda (PCT) and Erythropoietic porphyria are cutaneous porphyrias. Cutaneous porphyrias cause skin symptoms due to photosensitivity. Two porphyrias have both neurovisceral and cutaneous symptoms namely, Hereditary coproporphyria (HCP) and Variegate porphyria (VP).Congenital erythropoietic porphyria is rare autosomal recessive subtype of porphyria manifesting in infancy and childhood with reddish colour of urine and hypersensitivity of skin to sunlight which leads to blistering, severe scaring, hyperpigmentation and increased hair growth[2] .Malformation of fingers and nails occur and patient becomes anemic due to shortened life span of RBCs. Brownish and reddish discoloration of teeth occurs (erythrodontia)which fluorescence under ultraviolet light .Diagnosis can be suspected based on clinical presentation and can be substantiated by finding increased levels of porphyrias in urine. Diagnosis is confirmed by measuring the specific UROS enzyme activity.[3]

CASE REPORT

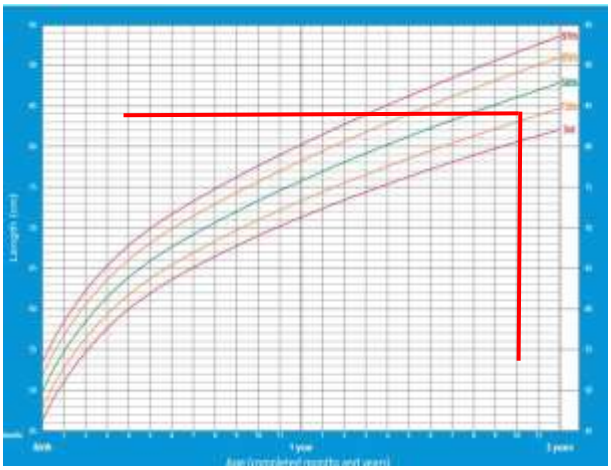
This case report is about 17 month old boy who presented with complaints of reddish discoloration of urine, sclerodermatous rash on sun exposed areas and acrolysis of soft tissues. Symptoms began on first day of life when his mother noticed reddish discoloration of urine which was not associated with any other urinary complaint. At 2

months of age he started developing vesicles initially on tips of fingers which later progressed and involved the sun exposed areas of body by 5 months of age including hands, feet and face. Eruption of these vesicles led to desquamation and scarring of skin at 5 months of age but for last few months due to repeated ulcerations, his skin had become fragile and sensitive to even mild trauma. During his course of illness he visited multiple health facilities and general practioners. Meanwhile multiple blood tests and urine tests were done but precise diagnosis was not made. He has had 8 blood transfusions. He was advised to avoid sunlight and topical sun blocks were advised but symptoms persisted. He was completely vaccinated according to EPI schedule. He was 2nd child of the consanguineous marriage with significant family history anthropometric measurements revealed weight for age on 15th percentile and length for age below 3rd percentile





Weight for age: 15th percentile



Length for age: below 3rd percentile

His nose and cheeks were badly scarred with areas of hypertrichosis especially over forehead and cheeks along with depigmentation of sun exposed areas (fig 1). Under the visible light his teeth were copper red (fig: 3) .Atrophic scars were present on dorsum of hands and feet and face, with mutilating deformities of fingers. Abdominal examination revealed nontender soft hepatomegaly 3 cm below costal margin and splenomegaly 3 fingers below costal margin .Other systemic examination was unremarkable. Slit lamp examination was unremarkable. The

early onset of illness with skin manifestations and mutilation of fingers were highly suggestive of CEP. The patient was investigated. His CBC revealed low hemoglobin with relatively high retic count. Liver and renal function tests were normal. 24 hour porphobilinogen (PBG) was normal. However 24 hour urinary level of uroporphyrin and coproporphyrin were elevated. So the diagnosis of CEP was confirmed .Sun protection was advised and oral *B*-Carotene 15 mg/day was prescribed.

Fig 1: Picture of face showing hypertrichosis, atrophic scars and depigmented skin lesion.

Fig 2: Reddish discoloration of urine.

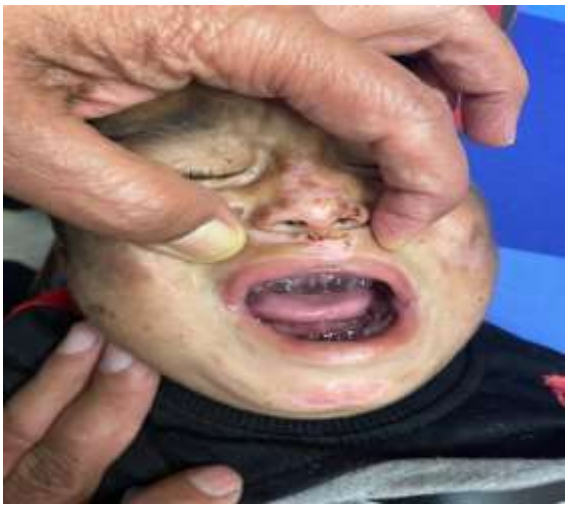


Fig 3: Erythrodontia (copper, red colored teeth).

Fig 4

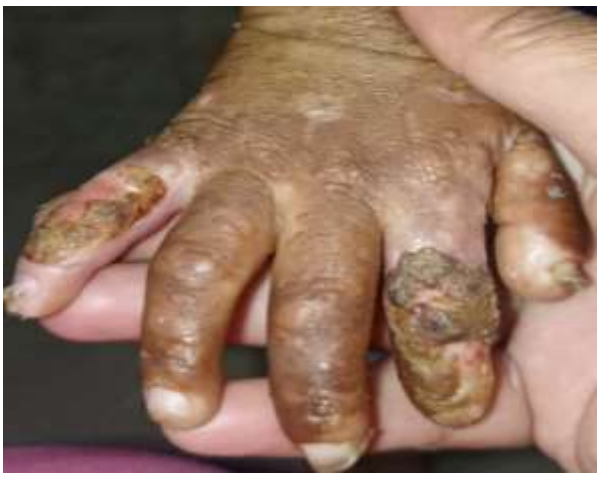


Fig 5

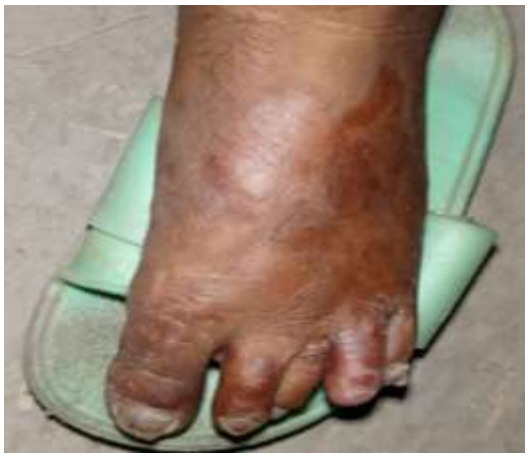


Fig 4,5,6: Mutilation of fingers and toes

Investigation:

	Investigation	Results	
1	CBC	22/07/2023	22/08/2021
i	HB	9g/dl	6g/dl
ii	RDW	21.6%	16.4%
iii	WBC	8.7x10^9/L	5.98 x 10^9/L
	Neutrophil	21.4%	25.7%
	Lymphocytes	64.9%	62.7%
iv	Platelet	186X10^9 /L	65x10^9 /L
4	Peripheral smear	Anisocytosis, microcytosis	
5	Serum ferritin	45.0ng/ml	
6	G6PD deficiency	Negative.	
7	Coombs test		
	Direct	Positive	
	Indirect	Negative	
8	Retic count	4.06%	
9	Urine examination		
i	Urine uroporphyrin	98455nmol/24hrs (reference range <30)	
ii	Urine coproporphyrin(24 hours)	48812nmol/24hr (reference range<230)	
10	Serum Anti Ds DNA (IgG)	4.44 IU/ml	
11	ANA	Negative	
	Anti-smooth muscle antibodies(ASMA)	Negative	
	Antimitochondrial antibodies (AMA)	Negative	
12	Ultrasound	Hepatosplenomegaly	

Haem biosynthetic pathway showing the site of enzyme deficiences in the different porphyrias

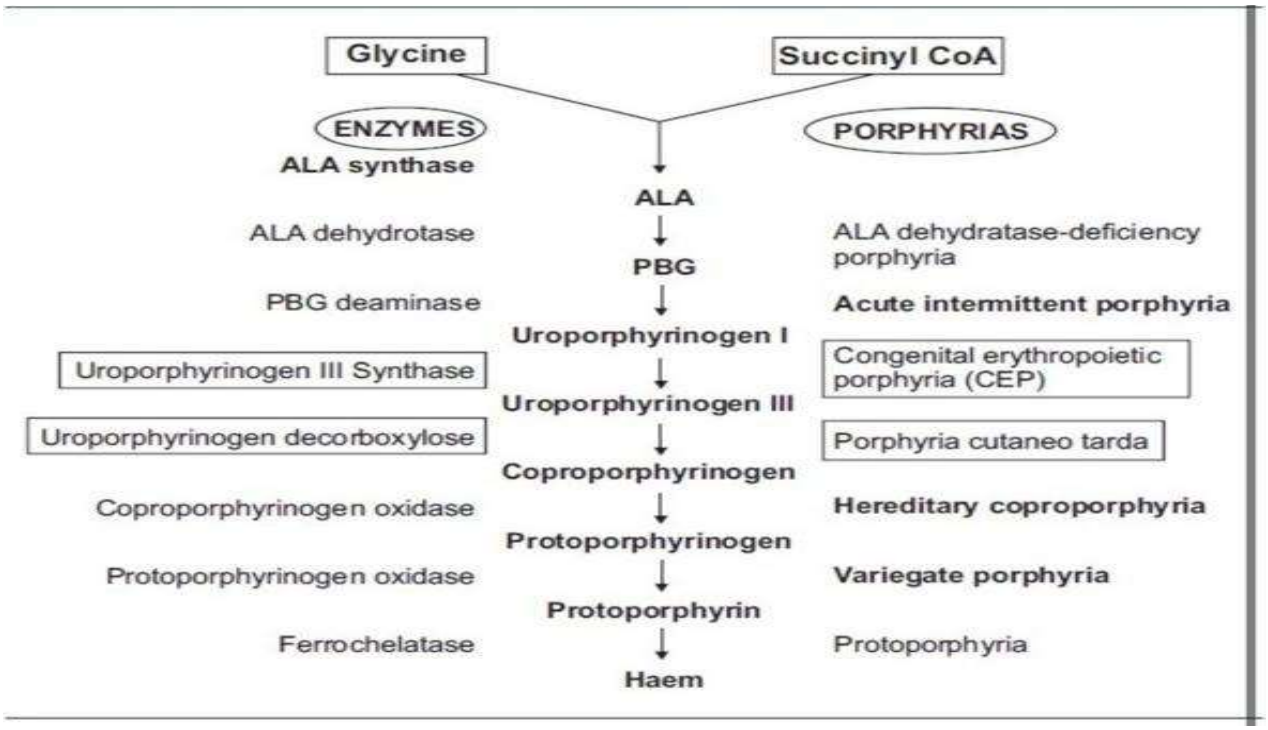


Fig 7 : Haem biosynthetic pathway showing the site of enzyme deficiences in the different porphyrias[4]

DISCUSSION

Congenital erythyropoietic porphyria (CEP) is the rare but more serious type of porphyria .The basic abnormality is uroporphyrinogen III synthase (UROS) gene defect in the process of erythropoiesis in the bone marrow. This defect results into disordered synthesis of urobilinogen to uroporphyrinogen II, due to complete or partial deficiency of UROS enzyme, which leads to excessive production of uroporphyrinogen I and coproporphyrinogen. These protoporphyrins are extremely photoreactive and induce formation of free radicals that lead to cell death due to photooxidation.[5] This effect is multiplied when exposed to wavelength of 400-420 nm. Blisters forming over the sun exposed areas are characteristics of congenital erythropoitiec porphyria .Vesico-bullous lesions on sunexposed areas, hypertrichiosis, spotted atrophic scars, sclerodermatous rash are the features shared by bullous porphyrias.[6] Brown teeth and bone marrow, red coloured urine and hemolytic anemia are the other notable features. The porphyrin profile of the urine mainly uroporphyrinogen I and coproporphyrinogen I helps in diagnosis .Detection of C73R gene mutation indicated severe deficiency of the enzyme uroporphyrin synthase.[7] Reticulocytosis, bone marrow hyperplasia and red blood cells emitting red fluorescence in the bone marrow and peripheral blood are supportive of CEP. Wide heterogenicity in the age of onset, severity of symptoms and their duration is the hallmark of CEP and it also results in a notable delay in diagnosis of CEP. In our case, the symptoms developed very early. Presentation was typical of CEP. Genetic testing though couldn't be performed but reddish discoloration of urine, which was the initial symptom in our case and the typical skin manifestations were suggestive of CEP. This early onset also is indicative of severe disease. In a series of CEP patients, approximately 76% of children had early onset with urine discoloration and cutaneous manifestations.[8] Neonatal jaundice and transfusion dependent hemolytic anemia are indicative of severe disease.[9] Our patient had evidence of hemolytic anemia requiring multiple transfusions. There was evidence of hyperspleenism as well. All these features indicate severe CEP. There are reported cases of disease presenting in later childhood or in adulthood with mild cutaneous manifestations. This shows greater phenotypic heterogeneity.[10] Vitamin D therapy, photo protection, chronic transfusions and bone marrow transplantation are the mainstay of the treatment.[11,12] Oral activated charcoal is helpful in some cases. Cimetidine inhibits heme synthesis and may decrease skin manifestations. Only curative treatment is bone marrow transplant (BMT) or hematopoietic stem cell transplantation (HSCT).Its widespread application has been limited due to associated significant morbidity and mortality and due to its limited availability. Only supportive treatment could be offered to patient. This child is now 3 years old and has been advised sun protection, VitD supplementation, cimetidine at dose of 30mg/kg/day in three divided doses[13] and B-carotene in a dose of 15-180 mg/day.

Conflict of interest:: None.

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