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Congenital Galactosemia: About 5 Cases

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Summary

Congenital galactosemia is an autosomal recessive hereditary metabolic disease characterized by enzymatic deficits in the metabolism of galactose. This is the interest of our study.

This is a retrospective study of 5 cases of congenital galactosemia in the neonatal medicine and intensive care unit. We studied the main clinical signs, the age of onset of symptoms, and the therapeutic management.

The median age of admission of the newborns was 5 days, there was a 4 boys and 1 girl. In 4 cases, the clinical signs appeared between 4th day and 7th day of life, dominated by jaundice, hepatomegaly and neurological signs. The notion of consanguinity was found in 4 cases and similar cases in siblings in 2 cases. Breastfeeding was exclusively maternal in 4 cases. The biological assessment showed hyper bilirubinaemia with hepatic cytolysis in all cases and a descreased prothrombin level in 2 cases. The positive diagnosis is made by the demonstration of the accumulation of galactose -1- erythrocyte phosphate (spot test) and the confirmation of the enzyme deficiency. The evolution under diet without galactose was favourable in 4 cases.

Congenital galactosemia is a hereditary disease with autosomal recessive transmission, the prognosis depends on early diagnosis and therapeutic management, hence the need for the establishment of systematic neonatal screening and antenatal diagnosis in families at risk.

Introduction

Congenital galactosemia is an inherited autosomal recessive metabolic disease characterized by enzymatic deficiencies in the metabolism of galactose. Galactose-1-phosphate uridyltransferase (GALT) deficiency is the most frequently encountered deficiency, giving rise to an accumulation of galactose-1-phosphate [1].

Patients and methods

This is a descriptive retrospective study of 5 cases of congenital galactosemia. The collection of data was carried out according to the clinical files in the neonatology and neonatal care unit department at the mother-child hospital Abderrahim Harouchi CHU Ibn Rochd Casablanca-Morocco.

The parameters studied for each patient were the age at onset, the history, the clinical and biological signs, the diagnosis of certainty as well as the complications and the methods of management.

Observation 1: This is a new born male with exclusive breastfeeding. He was admitted on 14th days of life for late jaundice evolving from D7 of life. The new born is born of a first-degree consanguineous marriage. The clinical examination found a jaundiced new born, hepatomegaly without splenomegaly without digestive disorders associated with axial and peripheral hypotonia, backward head rejection and archaic reflexes present. The assessment showed hepatic cytolysis with ASAT=635UI/L, ALAT=247UI/L, hyperbilirubinemia at 379 mg/l with mixed predominance (BL: 199 mg/l, BC= 180 mg/l), normal TP at 90%, Normal blood sugar at 0.63 g/l. The ophthalmological examination found a bilateral congenital cataract. Galactose transferase activity was undetectable in red blood cells. The patient was fed with milk without galactose then a diet completely devoid of galactose was well followed. The evolution was marked by the rapid disappearance of jaundice with normalization of transaminases and good staturoweight and psychomotor development over a long period of time term.

Observation 2: This is a newborn female exclusive breastfeeding. She was admitted for prolonged jaundice noted on D5 of life associated with diarrhoea, vomiting and refusal to breastfeed. The parents were first degree consanguineous. The clinical examination found a hypotonic newborn with weak archaic reflexes, who presents with generalized mucocutaneous jaundice, significant hepatomegaly without splenomegaly. hyperbilirubinemia at 166 mg/l with mixed predominance with BL=94mg/l, BC=71mg/l, a normal TP at 75%. The dosage of Galactose -1-Phosphate uridyltransferase was not detectable. The ophthalmological examination returned normal. The evolution was favourable under diet without galactose.

Observation 3: A new born male was admitted on 6 th day of life for late jaundice associated with vomiting and refusal to breastfeed. Having a history of first-degree consanguinity, a brother who died at the age of 6 months in a context of prolonged jaundice. The newborn was under exclusive breastfeeding. The clinical examination found a jaundiced new born with hepatomegaly without neurological signs. the biological assessment showed hepatic cytolysis: ASAT=175UI/L, ALAT=95UI/L, hyperbilirubinemia at 95mg/l with mixed predominance and a normal PT at 58%. The ophthalmological examination did not note any cataracts. Galactose transferase activity was undetectable in red blood cells, galactose 1-phosphate assay greater than 1000 micromoles/litre thus confirming the diagnosis of congenital galactosemia. The patient was fed milk without galactose and then put on a diet completely lacking in galactose. The evolution was marked by the disappearance of jaundice and the normalization of hepatic transaminases with good psychomotor development.

Observation 4: A newborn male exclusively breastfed. He was admitted on 4th day of life for generalized jaundice accompanied by a haemorrhagic syndrome made of hematemesis. The new born is from a non-consanguineous marriage. The clinical examination found an icteric new born, pale without purpuric spots with bleeding at the puncture points, hypotonic with weak archaic reflexes, there was no hepatomegaly or splenomegaly. The liver test objectified hepatic cytolysis ASAT=250 IU/L, ALAT=221UI/L with hyperbilirubinemia at 80 mg/l predominantly free at 68 mg/l, a low PT at 28% and prolonged TCA at 65 seconds with a factor V decreased to 16%. The dosage of galactose -1phosphate was high with normal GALT activity and low galactose epimerase activity. The ophthalmological examination was without abnormalities. The patient was fed with galactose-free milk. The evolution was marked by the rapid disappearance of jaundice with normalization of transaminases. In the long term the patient developed a language disorder.

Observation 5: A newborn male under mixed breastfeeding admitted on D18 of life for neonatal hypotonia with a history of first-degree consanguinity and a brother who died on D9 of life in a context of jaundice. The clinical examination found a drowsy, hypotonic new born with absent archaic reflexes and a weak cry. He presents with intense generalized jaundice associated with hepatomegaly and signs of sepsis. The liver test showed hepatic cytolysis ASAT= 189UI/L, ALAT=201UI/L associated with hyperbilirubinemia at 250mg/l with a predominantly mixed mix. The haemostasis assessment objectified a low TP at 30%, an elongated TCA at 52 seconds and a low V factor at 33%. The cytobacteriological examination of the urine showed the presence of E. coli. Cerebrospinal fluid was normal with normal cerebral CT. Faced with this picture of E. coli sepsis with a urinary starting point and given the history of death in the siblings, a Spot test was carried out which returned positive confirming the accumulation of galactose-1-phosphate in the intra erythrocyte. The new born was put on milk without galactose and antibiotic therapy. The death of the patient was deplored in a context of severe sepsis.

	Observation 1	**Observation 2**	**Observation 3**	**Observation4**	**Observation 5**
Sex	**Male**	**feminine**	**Male**	**Male**	**Male**
Age of onset of symptoms	7th day of life	5th day of life	6th day of life	4th day of life	D18 of life
Personnal and family history	1st degree consanguinity	consanguinity first degree	-First degree consanguinity -Brother died in a context of jaundice	- No inbreeding -No pathological history	- 1st degree consanguinity - brother died in a context of jaundice
Type of breastfeeding	Exclusive maternal	Exclusive maternal	Exclusive maternal	Exclusive maternal	Mixed breastfeeding
Liver damage	Jaundice Hepatomegaly	Jaundice Hepatomegaly	Jaundice Hepatomegaly	Jaundice No HPM	Jaundice Hepatomegaly
Digestive impairment	No digestive problems	Difficulty breastfeeding, vomiting diarrhea	Suckling difficulty vomiting	No digestive problems	No digestive disorder
Neurological impairment	Hypotonia throwing the head back	Hypotonia	Normal neurological examination	Weak archaic reflex hypotonia	Hypotonia weak cry archaic reflexes absent
Ophthalmological examination	Bilateral cataract	Normal	Normal	Normal	not done
Hepatic check	Hyperbilirubinemia Hepatic cytolysis	Hyperbilirubinemia Hepatic cytolysis	Hyperbilirubinemia Hepatic cytolysis	Hyperbilirubinemia Hepatic cytolysis	Hyperbilirubinemia Hepatic cytolysis
Hemostasis assessment	Normal	Normal	Normal	Dicreased	Dicreased
Enzyme activity assay	Galactos-1-P uridyl transferase not detectable	Galactos-1-P uridyl transferase not detectable	Galactos-1-P uridyl transferase not detectable	undetectable galactose epimerase	Positive spot test
Evolution	Good height-weight and psychomotor development	Good height-weight and psychomotor development	Good height-weight and psychomotor development	Language disorder	Deceased

Table N 1: Summary table of the 5 observations.

Discussion

Congenital galactosemia is an inherited metabolic disease characterized by the presence of galactose in the blood due to metabolic incapacity. It is due to point mutations in one of the 3 enzymes of galactose metabolism: galactokinase, uridine diphosphate (UDP) galactose -4-epimerase and galactose -1-phosphate uridyl transferase (GALT).

The consanguinity of the parents and similar cases in the siblings constitute risk factors for congenital galactosemia [2].

Congenital galactosemia manifests early in the neonatal period, from the second week of life. The clinical picture is variable consisting of jaundice which is a frequent and early sign, of moderate intensity and prolonged duration. Hepatomegaly which is an evocative sign palpable between the 5th and 6th day of life of variable consistency [3]. A refusal to suckle and digestive disorder have also been reported [4] as is the case in observation No. 2 and 3. The ocular involvement is manifested by a bilateral cataract in droplet of oil which are nuclear opacities typically observed in children with galactosemia (figure 1), one can have other forms such as posterior subcapsular cataract or small size nuclear [5]. It develops in the first weeks of life, and can even exist at birth.

Congenital galactosemia can also give rise to a haemorrhagic syndrome due to hepatocellular insufficiency consisting of hematomas at the puncture sites, digestive or pulmonary haemorrhages or even haematuria [6]. Neurological signs can be early made of hypotonia with drowsiness or agitation with seizures. It is well known that the neurological future of galactosemic patients is not always good, some observations in the literature differ significantly from the results of our study, two observations concern adults who have developed neurological complications; one developed comitiality at age 30 and the other developed ataxia and apraxia. Bohles et al. report the observation of two galactosemic twins who presented with cerebellar and extrapyramidal disorders at the age of 12 years [7]. In addition, one can have ovarian disorders due to delayed puberty, primary or secondary amenorrhea, which can occur even under a well-monitored diet [9]. Bone involvement is common, such as osteoporosis, it can exist in children and adults of both sexes. Congenital galactosemia also predisposes to severe infections, of early onset, mainly Escherichia coli pyelonephritis, as was the case in our study.

Biological signs of orientation include an increase in liver enzymes testifying to hepatic cytolysis and hepatocellular insufficiency with a decrease in coagulation factors II, V, V, II, X associated with Hyper bilirubinemia.

Positive diagnosis is based on determination of reduced enzymatic activity of erythrocyte uridyltransferase (GALT) and estimation of galactose -1- phosphate. The specific detection of galactose 1 phosphate (Gal-1-phosphate), galactose and galactose uridyldiphosphate (UDP-Gal) confirms type I, II or III of congenital galactosemia. The interest of molecular analysis consists in specifying the genetic anomaly and facilitating genetic counselling.

When the diagnosis of congenital galactosemia is made, a strict galactose-free diet is prescribed which allows the healing of liver failure and associated clinical signs as well as the prevention of cataracts. During infancy, the milk diet is replaced by easy-to-use milk substitutes. Food diversification requires great vigilance and knowledge of the composition of the different foods concerned to avoid introducing foods rich in galactose. The education of galactosemic children and their parents is fundamental, it is based on the interest of the galactose-free diet. Genetic counseling is fundamental, parents must be informed of the genetic character of the disease, the clinical course of the disease as well as the risk of having other sick children as well as the interest of monitoring future pregnancies for an early care. [10].

The prognosis of the disease is gloomy, in the absence of treatment death occurs in a few days most often in connection with sepsis due to E. coli as is the case in our study where a newborn died by a severe E.coli sepsis [11]. Some studies find that galactosemia negatively affects the quality of life, according to the results of the survey carried out by BOCH et al, children from 8 to 15 years old have a lower intellectual score than the general population [12]. In our study, 3 of our patients had good height-weight and psychomotor development, while the 4th patient developed a language delay.

Patients with galactosemia should be followed throughout their lives. According to the National Health Service in England It is recommended to monitor [13,14]: Weight, height and head circumference, the existence of hepatomegaly, neurological and psychomotor development, the existence of cataracts and biological parameters, namely liver function, coagulation factors and hormonal balance.

Conclusion

The diagnosis of congenital galactosemia should be considered in a neonate of consanguineous parents who presents with prolonged jaundice with hepatic cytolysis. The clinical manifestations appear in the neonatal period from the ingestion of milk. It results in liver failure with jaundice, hepatomegaly, hypoglycemia, neurological and ocular signs which manifests as a bilateral cataract in oil droplets and the frequency of E. coli infections. The determination of the enzymatic activity of galactose remains the key element for the confirmation of congenital galactosemia. Management is based on a diet without galactose.

The prognosis depends on early diagnosis and therapeutic management, hence the need for systematic neonatal screening and antenatal diagnosis in families at risk.

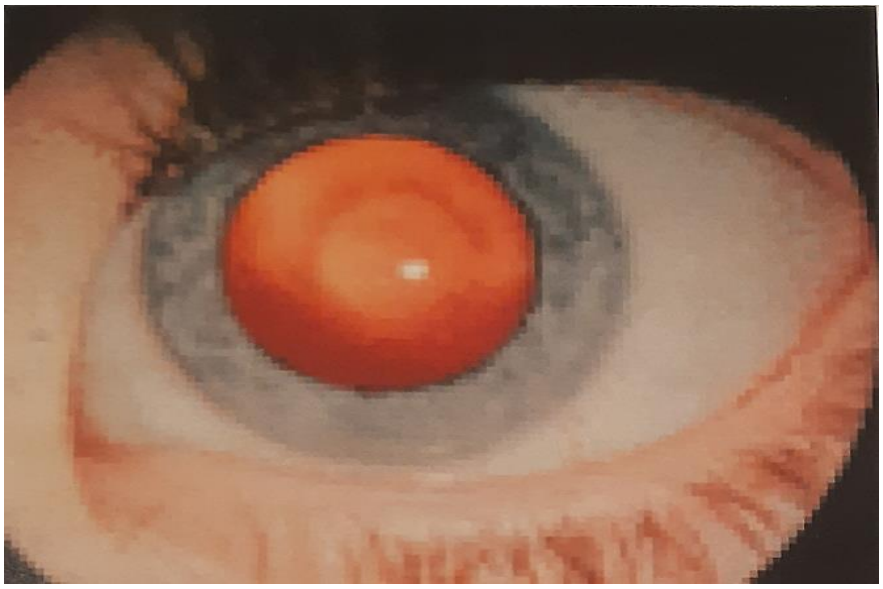

Figure 1: Oil droplet cataract [5].

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