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Von Giereke Disease : A Cause of Short Stature

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Abstract: *Glycogen storage diseases are pathologies that affect the glycogen metabolism. Several types were identified. The most common one is glycogen storage disease type 1 (GSD I) also called Von Giereke disease. It results from deficiency of the enzyme glucose-6-phosphatase, and it is observed in one of 100,000 births. Clinically it includes hepatomegaly that give an appearance of abdominal distension contrasting with slender limbs, fasting intolerance, epistaxis and repeated infections. Growth retardation and delayed puberty can frequently be observed in this pathology. We report the cases of two sibling children admitted to ourdepartment for evaluation of short stature which proved to be secondary to***.
Keywords: *hypoglycemia, delaystature, glycogen storage diseases, hepatomegaly, CT-guided biopsy*

I. Introduction

Hereditary disorders of carbohydrate metabolism are rare diseases. They can be diagnosed in a pediatric age on the occasion of metabolic complications or be encountered later in adulthood with their multifocal attempt. Among them, glycogen storage diseases (GSD) dominate. They include several diseases, all caused by inherited defects of enzymes involved in glycogen synthesis or degradation. These defective enzymes lead to abnormal glycogen concentrations in the tissues or abnormal glycogen structure.[1] Patients with these disorders haven't the capacity to produce enough glucose in the blood and use it as energetic substrate.

In absence of treatment , the result is many épisodes of acidosis and hypoglycemia and a toxic intracellular accumulation of glycogen in several tissues especially liver, kidney and muscles.[2]

We report the cases of two young brother and sister whose diagnosis of GSD was made late, despite an evocative symptomatology from early childhood.

Two patients, a brother(AS) and a sister (AD) respectfully aged 17 and 18, issued from a consanguineous marriage were hospitalized in the endocrinology department for evaluation of short stature and delayed puberty . The medical interrogatory reveal the death of a younger brother at age 9 in occasion of severe and recurrent hypoglycaemia and a high birth weight in both cases.

The history of the disease dates back to the birth marked in the two cases by iterative hypoglycemia treated symptomatically associated with episodes of epistaxis in the girl not explored before. The evolution was marked by the spacing of hypoglycaemia from the age of 10 years. In the absence of pubertal development in AD , parents consult and are oriented to the Endocrinology department.

The examination of the brother revealed the same clinical aspect. They were hospitalized for exploration Clinical examination revealed a severe and harmonious stature in both patients (AD: Size: 1-3DS/TM / TC ; Pd < P25 , AS: Size: -4 DS / TM / TC . weight < P5) , abdomen distension, a painful hepatomegaly (liver arrow in AD 15 cm and 17cm in AS) and a total impuberism . he remainder of the physical examination was unremarkable except for a feeling of inferiority and extreme shyness.

A biological assessment is then performed revealing an inflammatory syndrome and a delayed bone age in both patients. BN had cytolysis and cholestasis liver with a major mixed hyperlipidemia (Table I).

Hormonal exploration showed no endocrine dysfunction outside of a functional hypogonadotropic hypogonadism (Table I)

Both patients benefit of an abdominal CT scan . The boy had steatosic liver with an increased volume , seat of a large mass 12/07cm , well limited, spontaneously hyperdense , with heterogeneously enhancing by the presence of hypo dense span . This mass laminate the hepatic vein which stay permeable. Down, it compresses and displaces the stomach without border separating place. Three other nodular formations are associated with a late wash out in segment III (13) mm , IV subcapsular measuring 9mm and segment VII measuring 27mm , with blurred lines raised at periphery and homogenizing at late time.

We noted the presence of adenomegalies in left internal iliac and mesenteric territory. The most voluminous (12/10mm) was in the ileo territory. The bile ducts present no abnormalities as kidney and pancreas (fig1) . in front of the suspect

aspect of hepatic masses , a CT-guided biopsy was performed eliminating malignancy and allowing the diagnosis of hepatic glycogen storage (Fig. 2)

The radiological exploration of the sister showed an increased liver size with regular contours without focal lesion. The kidneys measured 109/56/55mm right et44/21/15 mm left. This one had a reduced size with a cortical index slightly clouded and seat of pelvic calculi (14 mm) and dilated calices ball upstream

The diagnosis of glycogen storage disease type I is based on the combination of clinical and biological suggestive arguments. Molecular analysis of the gene encoding for glucose 6 phosphatase witch allows the definitive diagnosis couldn't be performed.

The cardiovascular evaluation and otorhinolarygologic review looking for deafness was without abnormalities. Bone densitometry revealed an osteopenia in both cases . Therapeutically, both patients were placed on dietary enzyme therapy associated to a low-fat treatment in boy case. Clinical, biological and radiological monitoring is recommended in both cases.

II. Discussion

GSD are rare diseases that regrouping more than 12 heterogeneous clinical entities . Their incidence is one case per 20 000 à 43 000[3]. These are inherited autosomal recessive disease. They are Classified by numbers (GSD I to IX) in chronological order of discovery of the enzyme deficiency . However, they are also known according to the enzyme deficiency and thus classified as hepatic glycogen storage, more frequent in children (80% of GSD) and muscle glycogen storage , more frequent in adults.[4] The first description of the disease returns to Von Gierke in 1929. [1] In 1952, the enzyme deficiency was discovered by the Cori, husband and wife.[5] Their discovery was the first demonstration that a metabolic disorder could be caused by a deficiency of an enzyme.

Currently, GSD -I represents approximately 25% of cases diagnosed in the GSD in USA. In Europe, its incidence is approximately 1 in 100,000 live births.[6]

Glycogen is found in many tissues, especially in liver where it is the storage form of glucose and muscles constituting an energy reservoir. Thus, an enzyme deficiency on glycogen metabolism is responsible for overload hepatic glycogen (hepatic glycogenosis) or muscle glycogen (muscular glycogénosis) even two tissues.[7]. When glucose levels decreased in normal subjects , hepatic glycogen is rapidly degraded (glycogenolysis) to provide glucose leaving the liver cell and enters the blood. This process allows the maintenance of glucose roughly constant between meals, at night, or during prolonged fasting.

G6Pase deficiency leads to the liver inability to convert G6P to glucose. Glucose is stored in the liver as glycogen , and not used . Therefore severe hypoglycaemia occur very few hours after meal. This is particularly observed in the infant and small child, or when illness prevents a normal diet or causes vomiting or diarrhea . In response to the diminution of blood glucose , some hormones , especially glucagon and noradrenaline increase. These signais cause an increase in the lactic acid , fats (mainly triglycerides), and uric acid in the blood. Lipids leached from accumulated fat reserves and the excess of glycogen in liver are responsible of a considerable enlargement of the liver. It should be noted that many other liver functions are normal and patients with GSD -I don't develop liver failure, as in other inherited metabolic liver disease.[2] The enzyme system G6Pase actually comprises several components (subunits) required for normal function. The clinical picture will be oriented according to the type of infringement. In the absence of treatment, the blood levels of triglycerides and free fatty acids are very high. Cholesterol and phospholipids are moderately high with the appearance of yellowish plaques (eruptive xanthomas) on eyelids, elbows, knees and buttocks.[8] The severe hypertriglyceridemia is exceptional. It can lead to pancreatitis.[7]

Deficit G6Pase in the kidneys is responsible of hypertrophy. In the absence of therapeutic management, proximal tubular damage can occur with leakage of phosphates, potassium and amino acid in the urine. This functional abnormality of the tubules kidney is reversible if proper treatment corrects metabolic disorders.[8] Treated children usually have no renal symptoms except an increased glomerular filtration rate.

From adolescence, albumin level can increase in the urine that we have to research by an automatically microalbuminuria measurement. When protein level excreted in urine is high, renal disease may be more severe with onset of arterial hypertension. This is caused by the development of glomerular sclerosis and segmental interstitial fibrosis, a situation that may progress to renal failure in young adult age.[9] Medical treatment with angiotensin converting enzyme inhibitors have reduced the deterioration of renal function.[10]

About glucose blood level, although hypoglycemia becomes less severe through age . A delayed diagnosis and inadequate treatment can leads to severe growth or puberty retardation. Bone involvement (osteopenia or osteoporosis) may rarely occur. The osteodensitometric examination should be part of the annual patients' monitoring. Several hypotheses have been proposed to explain this complication, but none has been verified.

For unknown reasons, some patients may also develop benign liver tumors. Usually, these adenomas are discovered in adolescence during a routine ultrasound examination of the liver. They're usually

asymptomatic. The possible regression or disappearance of the adenoma if the management of the patient is improved, is still highly debated and controversial. Adenomas can become malignant or bleed. Surveillance of theses adenomas with MRI or CT is necessary and must be coupled with a clinical examination and biological tests (Alpha fetoprotein) for a complete monitoring.[11,12] In some cases, surgical resection can be indicated and rarely , liver transplantation may be discussed in front of multiple adenomas if they accessible to a resection.

Besides clinical abnormalities described above , patients with a GSD- Ib have neutropenia associated with bacterial and fungal infections. This neutropenia is the result of a lack of neutrophils maturation in the bone marrow. Furthermore the circulating neutrophile function is abnormal . Besides the problem of repeated infections, some patients develop inflammatory bowel disease characterized by appetite loss, abdominal pain , diarrhea and weight loss . They may also have sores in the mouth and chronic gingivitis with risk of early loss of permanent teeth. Fortunately, neutropenia, inflammatory bowel disease and mouth ulcers respond well to treatment with granulocyte-colony stimulating factor (G-CSF).[9,10]

Finally, it should be noted that significant bleeding may occur during evolution, associated with platelet dysfunction. It may cause abundant epistaxis, and excessive bleeding during surgical operations. This bleeding tendency must be notified in the case of scheduled surgery.[13]

Before the genes isolation, a definitive diagnosis of GSD -I required a liver biopsy to demonstrate the enzyme deficiency. Currently genetic analysis of mutations represent a non- invasive method of diagnosis for most Ia and Ib patients, making liver biopsy unnecessary in most cases.

Genes involved in Ia and Ib types have been identified . the gene causing type Ia is located on chromosome 17 (17q12) and the gene type Ib on chromosome 11 (11q23). Many mutations have been identified. With gene cloning and the carrier of G6Pase G6P , genetic diagnosis GSD -I became possible and available in a few specialized laboratories.[14,15,16,17]

Glycogenosis treatment is essentially dietetic. The aim is to provide regular inputs of glucose as frequent as possible with a meal every 2-3 hours throughout the day and enteral nutrition with a constant rate at night in small children. This nocturnal nutrition can be established at birth for years, depending on the growth parameters, the clinical and biological monitoring. Il is necessary to introduce complex carbohydrates in the diet. For infants and young children, meals are fortified with glucose polymers / maltodextrin.

Enteral nutrition may be replaced by raw starch of maize (corn flour ®) given as late as possible in the evening and once at night, depending on the tolerance of fasting. It is proposed to adolescents from age 12 to 18 to allow an extended fasting of the day.[18]

In adults, it is advisable to take one or two meals (s) by night (s) . Concerning the choice of other carbohydrates, it's recommended to restrict lactose, fructose and sucrose. For patients carrying GSD type III with myopathy a hyper proteinated diet may be prescribed up to 20% energy. A significant hypertriglyceridemia should be treated medically. The occurrence of hypoglycemia and / or lactic acidosis requires an immediate hospitalization for intravenous infusion of glucose and bicarbonate.[19]. Vitamin and mineral supplements are also necessary.

Many treatments may be proposed to improve the life quality of patients, to treat the symptoms through a multidisciplinary care and to try to correct the enzyme deficiency . Liver transplantation is rarely indicated, except in cases of liver

complications. Thanks to advances in research in recent years (bone marrow transplant, enzyme injection, genetic research and gene therapy) , was hoping for a real effective treatment of the disease.

Conclusion

Hereditary abnormalities of carbohydrate metabolism correspond to a wide spectrum of metabolic diseases. They are most often treatable whereas untreated, they lead to severe complications.

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Figures

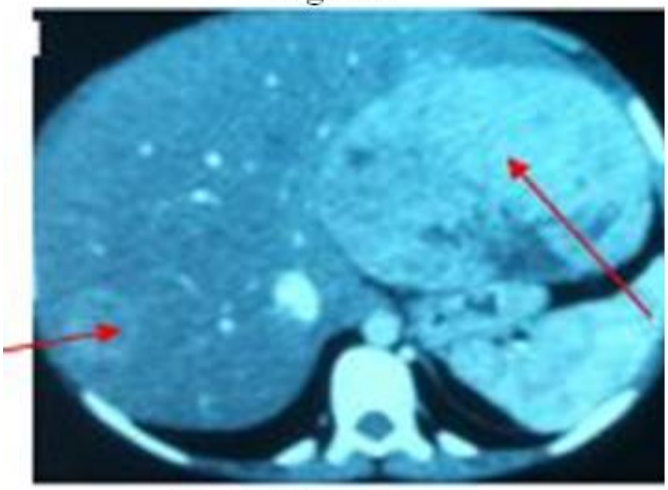

Fig1 : Liver tumors

Fig 2 : A Hepatic tumor proliferation of epithelial nature arranged in diffuse door spaces without evidence of separated fibrous fine septaB IHC ki67 of the population lower than 2% G X40

Table I: Paraclinical results

Parameter		Results	standards (units)
	BH	BN	
Liver function			
Gamma GT	60	838	21-58 U/l
AST	65	91	5-36 **Ul**/l
ALT	31	45	0-41 UI/l
Alkaline phosphatase	**92**	135	32-92 UI/l
ALBUMIN	40	46	35-50 g /l
kidney function			
Urea	0.16	0.15	0.15 à 0.45 g/l
Creatinine	7 .3		
	3.83		4,5 à 12 mg/l
NFS			
HB	9.7	12,7	14 - 18 g / 100 ml : Man ;12 - 16 g / 100 ml :
			80- 100 femtolitres
VGM	82.2	81 .9	40 - 52 % : Man ; 12 - 16 g / 100 ml : Woman
			4 000 - 10 000 /mm3
MCHC	33.3	32.3	150 000 - 450 000 /
	12000	**80 00**	
GB	268000		
PK	408000		
inflammatory balance			
VS			
First hour	20	30	Under 8mm
	54	60	Under 20mm
CRP	8	10	Under 6mg/l
Glycémie	**0, 6 5**	**0,76**	0,7-1 **g/l**
CHOLESTEROL	**2,**	**3.4**	**0-2 g/l**
TRIGLYCERIDES	**1,50**	**8.41**	**0.3-1.5 g/l**
CALCEMIE	9 6	88	**90-100 mg/l**
ACE	1	0,5	Under 5 Ug/l
Alpha foetoprotein	4.4	6.47	under 7 Ul/ml
B and C Hepatitis			
Bone age	10	11	years
TSH	2.	1,6	0.4-4 (UuI /ml)
FT4	1 9.	18	10-25 (P mol/l)
FT4 TSH	18 .6 16.4 3 .94 2.4		10-25 (Pmol /l) 0.4-4 (Uui/ml)
anti TPO antibody	0 9. 2		INF 12
CORTISOL	856 779.2 9		154-638 (n mol/l)
GH Before and after	0,2^22 0,4^28		0-20 (uU/ml)

GLUCAGON		
17OHP	1,2 1.28	1.5-7.2 (n mol/l)
SDHEA	8 10.8	80-560 (ug/dl)
DELTA 4	0,4 0.55	0.3- 3.1 (ng/l)
E2	76.76	55.05-260.57(p mol/l)
TESTOSTERONE	5.54	10.41-41.64 (n mol /L)
FSH	1.07 0.89	0.7-11.6 (mU/L)
LH	0.55 0.72	0.86-7.6 (mU /L)
PROLACTINE	11.03 8.83	5-25 (ng/ml)
PTH	13.9 14.7	12-72 (pg/ml)