Congenital Hyperinsulinism: Review of 12 Tunisian cases

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Hyperinsulinisme congénital du nouveau né et du nourrisson : Revue de 12 cas Tunisiens

LA TUNISIE MEDICALE - 2011 ; Vol 89 (n°04) : 369 - 373

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RÉSUMÉ

Prérequis : L'hyperinsulinisme congénital (HIC) est une affection hétérogène de point de vue génétique et réponse aux thérapeutiques. Les données se rapportant à cette maladie sont sporadiques en Afrique du nord.

But : Analyser les particularités cliniques et évolutives d'une série de 12 patients atteints et de soulever les difficultés diagnostiques et thérapeutiques liés à cette affection.

Méthodes : 12 observations d'HIC diagnostiqués entre 1989 et 2007 ont été analysées. Le diagnostic a été retenu sur des valeurs d'insulinémie ≥ 10μ UI/ml concomitantes à une glycémie < 3 mmol/l et /ou sur un rapport insulinémie/glycémie >0.3 et/ou un test au glucagon positif en hypoglycémie et ceci après avoir éliminé les causes transitoires d'hyperinsulinisme.

Résultats: Trois cas d'HIC étaient de révélation néonatale et neuf cas ont été diagnostiqués à un âge médian de 17 mois. Une hyper ammoniémie a orienté vers un hyperinsulinisme leucine-sensible dans un cas. Les circonstances de découverte étaient des crises convulsives chez sept patients, une encéphalopathie convulsivante dans deux cas et des malaises hypoglycémiques dans un cas. Sur 42 mesures de l'insulinémie réalisées en hypoglycémie, seulement 40% des insulinémies étaient ≥ 10μU/ml. Trois patients ont résisté au diazoxide et ont subi une pancréatectomie subtotale compliquée de diabète sucré dans deux cas et d'hypoglycémie persistante dans un cas; l'histologie a conclut à une hyperplasie diffuse des cellules ,. Le traitement a pu être arrêté chez quatre des huit patients répondeurs au diazoxide. Quatre enfants sont décédés et un taux important de séquelles neurologiques a été relevé : sept enfants ont un retard mental de sévérité variable et cinq ont une épilepsie séquellaire.

Conclusion : les résultats retrouvés confirment les difficultés de diagnostic positif et de traitement de l'hyperinsulinisme congénital. Les formes de révélation précoce étaient, comme rapportées dans la littérature, souvent résistantes au traitement médical. La proportion importante de séquelles neurologiques observée est liée à un retard diagnostic et/ou une chirurgie tardive et incite à instaurer une prise en charge précoce et agressive des hypoglycémies qui doit aller de pair avec l'enquête étiologique.

Mots-clés

Hypoglycémie, hyperinsulinisme, nouveau né, nourrisson, diazoxide, pancréatectomie, diabète sucré

SUMMARY

Background: Congenital hyperinsulinism in infancy (CHI) is a heterogeneous disorder with respect to genetics and response to therapy. Data on CHI are sporadic in North African population.

Aim: To characterize the clinical features and outcome of 12 Tunisian patients with CHI.

Methods: data of patients diagnosed with CHI during the period 1989-2007 were retrospectively analyzed. Diagnosis was considered whenever hyperinsulinemia ≥10μ UI/ml was concomitant to hypoglycemia < 3mmol/l and/or high insulin to glucose ratio > 0.3 and/or positif glucagon test. Transient causes of hypoglycemia, adrenal and growth hormone deficiency were excluded.

Results: There were nine infants diagnosed at a median age of 17 months and three newborns. Permanent hyperammoniemia, found in one patient, guided to leucine-sensitive hyperinsulinism. Seven patients presented with seizures, two with psychomotor delay and one with recurrent malaises. Among 42 assays of plasmatic insulin, when in hypoglycemia, 40% only were ≥ 10μU/ml. Three patients resisted to diazoxide and underwent subtotal pancreatectomy complicated by diabetes mellitus in two cases and persistent hypoglycemia in one patient. Histological examination concluded to diffuse hyperplasia of pancreatic cells. Diazoxide was discontinued in four out the eight responders' patients. Four patients died, seven patients developed variable degrees of mental retardation and five suffered from epilepsy.

Conclusion: Early onset forms were, as reported in the literature, mostly resistant to medical therapy. The high proportion of neurological sequelae is related to diagnosis delay or to a late surgery. We focus on the importance of a precocious diagnosis and aggressive treatment of hypoglycemia.

Key-words

Hypoglycemia, hyperinsulinism, newborns, infants, diazoxide, pancreatectomy, diabetes mellitus

Hyperinsulinemic hypoglycemia (HH) is characterized by the unregulated secretion of insulin from pancreatic ß- cells in relation to the blood glucose concentration [1]. Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in the neonatal and infancy period and expose to irreversible brain damage [1-5]. Two histopathological variants of CHI are individualized, the focal and the diffuse form which are clinically indistinguishable but genetically heterogeneous [1, 2, 6, 7]. Phenotype and genotype data of CHI were published in large series of Caucasian and Saudi children [7-10] but those in North African patients are sporadic[11, 12]. We report here the clinical and biochemical characteristics and the outcome of 12 Tunisian patients with CHI.

PATIENTS AND METHODS

We analyzed, retrospectively, the results of clinical, biochemical, radiological and histopathological findings of patients with CHI diagnosed in pediatric department of La Rabta Hospital during the period 1989-2007. Hyperinsulinemia was considered in either symptomatic or asymptomatic patients with persistent or recurrent anarchic hypoglycemias without ketonuria. Diagnosis was based on concomitant insulinemia ≥10 μUI/ml when glycemia <3mmol/l and/or on high insulin to glucose ratio ≥ 0.3 and/or when glycemia raised in response to 1mg intramuscular glucagon. Newborns with transient hypoglycemia were excluded (maternal gestational diabetes or fetal growth retardation). Adrenal and growth hormone deficiency were also excluded on normal adrenocorticotropin hormone essay, normal cortisol and growth hormone levels concomitant to hypoglycemia. Patients who declare first symptoms beyond 1 month of live were assigned to the onset infancy group.

RESULTS

Twelve patients (six males and six females) from 11 unrelated families were diagnosed with CHI during 18 years' period. Six patients were born to consanguineous parents. Two families were multiplex with 2 affected sibs. In one family (P3), the first child died from severe neonatal hypoglycemia and postmortem autopsy revealed cardiopathy. The mother of an affected child (P8) had a history of insulin hypersentivity in the childhood treated with punctual glucagon therapy. Five out of ten affected patients were macrosomic at birth with a median birth weight of 4300±1127 g (ranged 3000-6300g).

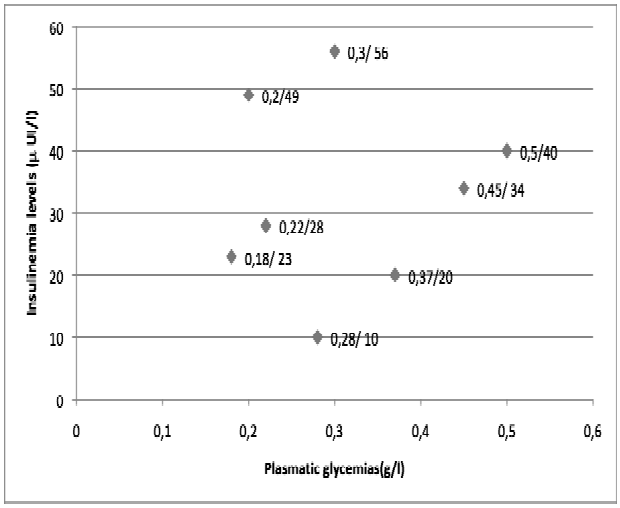
Three patients revealed in the first day of life and 9 patients presented first symptoms at a median age of 6 ± 4.09 months (range: 2-15 months). The age at diagnosis in this infancy onset group ranged from 3 to 64 months (median, 17 months). Only the half of the affected infants (4/9) were diagnosed before the first year of live although first symptoms appeared before this date in all but one of them. Diagnosis delay ranged from 1 to 59 months (median, 12 ± 18 moths).

Hypoglycemic seizure was the most commonly presenting symptom and was seen in seven cases. Four patients were referred for psychomotor delay and epilepsy, one of them had a history of perinatal asphyxia and was born with gangrene leading to forearm amputation (P9) and one was treated with hydrocortisone and growth hormone (P12). One patient presented with recurrent malaises during 8 months responding to oral sugar intake (P8). Mild hepatomegaly and was found in two patients (P6, P12) and 3 patients had microcephaly at diagnosis (P6, P11, P12). No facial dysmorphic features were specified in the medical records.

On biological investigations, hypoglycemias occurred both in the fed and fasting state and was asymptomatic in most patients although it was severe. Refractor hypoglycemias were noted in all neonatal onset patients. Recurrent daily hypoglycemias occurred also in five of infancy onset patients in whom high glucose intake was needed (>12 mk/kg/min)

Hyperinsulinemia was not easy to identify; indeed, among 42 plasmatic assays of insulin measured when glycemia was less than 3 mmol/l, only 40% were ≥ 10mU/ml. Insulin levels during hypoglycemia ranged from 10 to 56mU/ml. Insulin to glucose ratio (I/G) ranged from 0.35 to 1.86. There was no correlation between the serum insulin levels and the severity of hypoglycemia as illustrated in figure1. In P10, the insulinemias concomitant to hypoglycemia were always below 10mU/ml in spite of repetitive samplings; the diagnosis was based in this patient on I/G ratio at 0.35 and on positive glucagon test. Plasmatic C peptide measured in 4 patients was high only in one patient (P5). The ammonia concentration, measured in eight patients, was found permanently high in one patient (214μmol/l) and increased in post prandial consistent with a leucine sensitive HI (LSHI). Urinary chromatography of organic acids, analyzed in nine patients, was normal excluding deficiency of fatty acids ß-oxidation.

Figure 1 : Concomitant plasmatic glycemia and Insulinemia values



Abdominal computed tomography, performed in six cases, was normal. Cardiac ultrasound showed hypertrophic cardiomyopathy in 2 cases (P10,11), inter atrial defect (P3), and aortic valvular regurgitation (1 case).

Tableau 1 : Clinical, biochemical and outcome of affected patients

Patient	**P1**	**P_2 (sibP_1)**	**P_3**	**P_4**	**P_5**	**P_6**	**P_7**	**P_8**	**P_9**	**P_{10}**	**P_{11}**	**P_{12}**
Year of diagnosis	**2001**	**2002**	**2006**	**1983**	**1987**	**1997**	**1998**	**2001**	**2001**	**2001**	**2003**	**2006**
Age at first symptoms onset (months)	1st day	1st day	1st day	3	2	8	9	9	5	6	15	3
Age at diagnosis (months)	25 days	1st day	3	4	4	18	10	17	64	7	17	21
Birth weight (g)	4850	4720	5600	NA	6300	3800	3450	3250	4850	3000	NA	3200
Clinical presentation	seizures	systematic screening	seizures	seizures	seizures	seizures psychomotor delay	seizures	malaises	seizures psychomotor delay	seizures	psychomotor delay	seizures psychomotor delay
- Glycemia (g/l)	0.2	0.15	0.18	0.27	0.35	0.32[2]	0.19	0.35[2]	0.2	0.45[2]	0.4[2]	0.45[2]
- Insulinemia[1] (µU/ml) (min-max)	45	28	24	NA	18	(20-34)	49	(13-56)	14	All < 10 G/I ratio: 0.35	(10-17)	(12-34)
- Glucagon test		ND	ND	NA	NA	ND	+	+	ND	+	+	ND
Ammonaemia (µmol/l)	ND	32	44	NA	NA	10	ND	38	62	45	36	**214**
Glucose rate intake (mg/kg/min)	17	21	13	NA	NA	17	10	10	14	10	14	9
Diazoxide	No											
- dose (mg/kg)		20	10	NA	12	10	25	10	10	10	7	8
- duration therapy (m)		3	8		5	84	12	6	48 ongoing	72 ongoing	30	48 ongoing
- response		-	+		-	+	+	+	+	+	+	+
Hydrocortisone	+	+	+		+							
Pancreatectomy (age)	-	+ (3 m)	-	+ (4 y)	+ (9 m)	-	-	-	-	-	-	-
Psychomotor delay		mild	NA	severe	mild	moderate + deafness	-	-	severe	-	moderate	severe
Epilepsy		+	-	+	-	-	-	-	+	-	+	+
Mellitus diabetes (age)		-		+/ 14 y	+/ 10 m	-	-	-	-	-	-	-
Death (age)	+ (1 m)	+ (18 m)	+ (8 m)	+ (20 y)	alive	alive	alive	alive	alive	alive	alive	alive

NA: data not available, ND: not done, 1 : plasmatic insulin values at a plasma glucose <0.5g/l, 2: mean value of low plasmatic glycemias

All patients required high rates of glucose infusion varying from 9 to 21 mg/kg/ min (median: 14±3.95 mk/kg/min); first by parenteral then by continuous enteral feeding. Steroid therapy, prescribed in 4 patients, was ineffective. One patient required a continuous intravenous Glucagon therapy during several days (P2). Hypoprotidic diet associated to sodium benzoate were prescribed in the patient with leucine sensitive HI (P12).

Eleven patients received diazoxide at a median dose of 10 mg/kg/day (7-25 mg/kg/d); one patient (P1) died at one month of age before starting therapy. Response to diazoxide was obtained in 8 patients and therapy was discontinued in 4 of them after a median period of 21 months (6-84 months). An attempt to stop treatment failed in 3 children who still receive diazoxide since 4 and 6 years. Two cases developed hirsutisme with diazoxide, which disappeared after stopping treatment. One patient developed transient hyperuricemia and another

presented hydric retention (P3).
Three patients were resistant to medical therapy and required pancreatectomy respectively at the age of 4 years (France, 1986), 9 months (France, 1987) and 3 months (Tunisia, 2002). The preoperative pancreatic venous samplings (PVS), performed in the second patient, was inconclusive and a second subtotal pancreatectomy was indicated 3 months after the first surgery. In the third patient, PVS was technically impossible since splenic venous couldn't be catheterized; and thus resection was guided by extemporaneous histological study. Definitive histological study showed diffuse ß cells hyperplasia in all these patients.
After surgery, the first two patients developed diabetes mellitus, 10 years later for the first, and a few days later in the second. An exocrine pancreatic deficiency was diagnosed in the latter but was transient. A severe mental, motor sequelae and epilepsy complicated the outcome of the first patient who dead at 20 years of age. The second patient suffered from learning difficulties. Hypoglycemia persisted in the third patient and was partially controlled by dietary and diazoxide therapy; a complementary surgery was refused by the parents.
The death occurred in all patients with neonatal onset and was related to nosocomial sepsis in two of them. The third(P3) developed at 6 months of age subdural empyema controlled with antibiotherapy and then died at home at 8 months old.
Among the ten patients for whom we had sufficient hinsight recul, eight developed variable degrees of mental retardation. The most severe disability was observed in 3 cases. Five patients suffered from sequellar epilepsy. No visual impairment was demonstrated; auditory evoked potentials, performed in 4 patients (P6,9,10,11) showed deafness in one patient. Cerebral tomodensitometry performed in five patients showed brain atrophy in 2 patients. Table 1 summarizes the clinical, biochemical and outcome of affected patients.

DISCUSSION

CHI is a rare disorder occurring in one of 50.000 births in Western Europe. The incidence may be as high as 1/2500 births and most of the cases are familial in areas with high consanguinity such as in Saudi Arabia and Ashkenazi Jewish populations [7, 10]. In France, 95 % of CHI cases are sporadic [13]. The high rate of inbreeding in our cohort (54%) suggests a high frequency of this disorder in Tunisian population.
Most infants with CHI present during the 1st postnatal days and the others during the 1st year [2, 6, 8, 9]. The age at presentation is not influenced by the histological form; indeed, among 60 infants with focal form reported by Cretolle et al, 60% of cases had severe neonatal onset form [13]. The diagnosis in infants is often delayed [5,9]; as it was observed in our cohort, only the half of the affected infants (4/9) were diagnosed before the first year of live although first symptoms appeared before this date in all but one of them. Four among the nine infantile onset's patients had already neurological sequelae at diagnosis (P6,9,11,12). Diagnosis of CHI should be therefore considered in the investigation of psychomotor delay.
As reported in others series, macrosomia at birth was frequently noted and hypoglycemic seizure was the most presenting symptom although more subtle symptoms may be present [6, 8, 9]. Mild hepatomegaly can be noted and does not exclude the diagnosis [6, 9]. Hypoglycemia is usually persistent, severe and anarchic with low fatty acids and no plasmatic or urinary ketone [2, 3]. Profound hypoglycemias can be asymptomatic detected by routine monitoring of capillary glucose; this was noted in five of our patients [2]. The neonatal form is the most severe [9]. In our study, hypoglycemia was persistently very low in the five children diagnosed in the third trimester of life.
The high glucose requirement to maintain normoglycemia constitutes a diagnostic criterion (more than 8 mg/kg/min and up to 20-30 mg/kg/min); neonates required higher rates of glucose than infants in a serie of 175 cases CHI reported by De Lonlay et al. [1, 8, 9]. This condition was verified in our patients as median glucose intake was of 14 mg/kg /min.
The inappropriately raised serum insulin and peptide C levels for glycemias confirm the diagnosis of HI [1, 2, 14]; however, it is not often present in infants. In our experience, only 40 % of insulinemia values were more than 10 μUI/ml when hypoglycemia was noted. This proportion was to 20 % of 380 measures of insulinemia level in the 28 patients reported by De Lonlay et al [9]. This might be due to periodic release of insulin which is missed by a single sample or to a rapid hepatic clearance; so it's important to repeat samplings and to consider the I/G ratio more than the absolute level of insulinemia alone [1]. Genetically, CHI is a heterogeneous condition [1, 9, 17]. Recessive mutations in ABCC8 and KCNJ11 gene, which encode respectively the two subunits, sulfonylurea receptor 1"SUR1"and the inward –rectifying "KIR6.2" of the adenosine triphosphate sensitive potassium channels (K+ ATP), are the most common cause of diffuse CHI in newborns[7, 15]. Focal CHI result from a paternally inherited mutation on the ABCC8 or KCNJ11 gene and loss of the maternal allele restricted to the pancreatic lesion [16].
The leucine-sensitive HI, diagnosed in one of our patients is related to mutations in glutamate deshydrogenase gene. This disorder is rare, it was diagnosed in 12 of 69 tested patients in the French cohort during a 20 years' period [9]. HI Patients with this disorder present post-prandial and fasting hypoglycemia and permanent hyperammoniemia, neurological signs and epilepsy occur later in infancy and are not consequences of recurrent hypoglycemia [17]. Short-chain L-3-hydroxyacyl-CoA deshydrogenase deficiency was reported in severe familial diffuse forms of CHI [18]. Since these two metabolic disorders implicate specific therapies; they should be screened in patients with HI.
Treatment of patients with CHI must be prompt and aggressive in order to prevent irreversible brain damage; blood glucose level must be maintained above 3.5 mmol/l. A continuous Glugacon infusion (0.5-2 mg/day) should be administered if blood glucose levels remains unstable despite a high glucose rate [1, 6, 14]. Specific treatment is based first on oral diazoxide which acts by opening the K+ channels [1, 9]. Most neonatal forms are diazoxide resistant whereas the drug is usually effective in infants (60% of cases) and in leucine sensitive HI

[9, 17, 19]. In our serie, only one patient (P3) with early onset responded to diazoxide. Octreotide, an analog of natural somatostatin, should be tried before surgery in cases with diazoxide unresponsiveness [6, 14].

Although most of the patients treated medically remains dependent on medication, some may recover due to the increased ß-cell apoptosis. This justifies stopping medical treatment once a year under medical supervision [20, 21]. Remission was observed in 4 of our patients but 3 patients are still dependant to low dose of diazoxide.

Surgical treatment is required when medical or dietary therapies are ineffective or when a focal form is suspected [22]. Subtotal pancreatectomy exposes to postoperative hypoglycemia that required medical therapy or a second surgery as in P 2 and P5 [10, 13]. Diabetes mellitus (DM) complicated the surgery in a proportion of 45 to 85% and occured after a variable delay [22]. Thus, among the ten pancreatectomized patients reported by Cherian, seven developed DM after a period ranging from 7 to11 years [23]; one of our patients developed DM 10 years after the surgery.

The most serious complication of CHI neurological sequelae and/or epilepsy [4, 5, 24].The relatively high proportion of patients with disability in our cohort can be related to refractor hypoglycemias before surgery in two patients and to the late referral in the others in whom symptomatology was confusing. In two patients, perinatal asphyxia (P9) and hyperammoniemia (P12), worsened neurological prognosis. Cretolle et al reported 18 % of neurological disability in a serie of 60 French patients with HI [13] whereas psychomotor sequelae occurred in 42 % of Saudian child with CHI [10].

CONCLUSION

In spite of the small sample of patients included in this cohort, it was possible to characterize the phenotype of CHI. Clinical, biochemical features and response to therapy found in our patients were comparable to those reported in occidental or Saudian populations. The death of all 3 patients with neonatal onset illustrates the difficulty to manage HI in childhood. The frequency of neurological disabilitiy was related to the diagnosis delay in some patients. That's why neonatologists and pediatricians should have a high index suspicion of CHI in any patient with persistent hypoglycemia. Etiological investigations of CHI should include screening for metabolic causes that require specific therapy.

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