J Endocrinol Invest (2014) 37:1201–1209
DOI 10.1007/s40618-014-0139-9

ORIGINAL ARTICLE

Diagnostic pitfalls in the assessment of congenital hypopituitarism

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Received: 14 April 2014 / Accepted: 12 July 2014 / Published online: 1 August 2014

Abstract
Background The diagnosis of congenital hypopituitarism is difficult and often delayed because its symptoms are nonspecific.
Aim To describe the different clinical presentations of children with congenital hypopituitarism to reduce the time for diagnosis and to begin a precocious and appropriate treatment.
Study design We analyzed a cohort of five children with congenital hypopituitarism, describing their clinical, biochemical and radiological characteristics from the birth to diagnosis.
Results As first sign of the disease, all of five patients presented a neonatal hypoglycemia, associated in four cases with jaundice. In all these four cases, the clinicians hypothesized a metabolic disease delaying the diagnosis, which was performed in only two cases within the neonatal period. In the other three cases, the diagnosis was formulated at 2, 5 and 8 years of life because there was severe and precocious growth impairment.
Conclusions It is important to suspect congenital hypopituitarism in the presence of persistent neonatal hypoglycemia associated with jaundice and of a precocious and severe reduction of the growth velocity in childhood. In all these cases, it is necessary to undertake a hypothalamic–pituitary magnetic resonance imaging scan as soon as possible, and to start appropriate treatment.

Keywords Congenital hypopituitarism · Hypoglycemia · Neonatal jaundice · Growth impairment

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Introduction

Congenital hypopituitarism is a rare condition, present from birth, characterized by the underproduction of one or more pituitary hormones [1]. Diagnosis is often delayed because its clinical presentation ranges from absent to severe non-specific symptoms, and current laboratory tests lack sensitivity during the neonatal period. In particular, symptoms include hypoglycemia, which may sometimes result in a sometimes life-threatening neonatal emergency, with seizures, apnea and cyanosis; prolonged jaundice (with elevation of both conjugated and unconjugated bilirubin); dysmorphic feature with midline defects, ocular and craniofacial anomalies; and microphallus in males, often with undescended testes [2–4]. Birth size and weight are normal or moderately reduced, but they rapidly decrease with an important reduction in length in the first months of life [5]. In some cases, newborns may be initially asymptomatic but at risk of developing pituitary hormone deficiencies over time [2]. In all cases, careful evaluation of these patients is necessary to prevent the morbidity and mortality associated with untreated hormonal abnormalities [5–8]. However, hormonal assessment in the neonatal

period is difficult; in fact, age-correlated normative data are lacking at this age when contraindications are detected for some GH provocative tests [2, 9]. The main investigation necessary to achieve a definitive diagnosis is the magnetic resonance imaging (MRI) of the brain and the pituitary gland. It is helpful to research the etiology of hypopituitarism and any possibly associated structural anomalies [10]. Children with congenital hypopituitarism typically present the classic triad of pituitary stalk (PSA) interruption syndrome: an interrupted or thin PSA, an absent or ectopic posterior pituitary (EPP), and anterior pituitary hypoplasia or aplasia [11, 12]. Associated abnormalities may include optic nerve hypoplasia, absent septum pellucidum, agenesis of the corpus callosum, septo optic dysplasia and Arnold–Chiari I malformation [10]. Moreover, children with hypothalamic–pituitary structural abnormalities more frequently have severe phenotypes and multiplex pituitary hormonal deficiencies (MPHD) [13–16].

Most cases of congenital hypopituitarism are sporadic, but genetics may play a role [2]. Given that our knowledge of the genes that direct pituitary development or hormone production is continuously expanding, an increasing proportion of cases can be attributed to a specific genetic defect. The likelihood of finding mutations is increased by positive family histories and by association with a significant malformation of the pituitary gland [17]. In these cases, genetic analysis should be taken into account to reach a definitive diagnosis.

This brief report aims to evaluate in detail the clinical presentation of a cohort of five children with congenital hypopituitarism to draw attention to the warning symptoms, and consequently, to allow for a more rapid diagnosis and more effective treatment.

Patients

One patient was born in Verona, four in other peripheral hospitals in the Veneto region (Italy). All five children were referred to the Pediatric Division of the Hospital of Verona, Italy, for diagnosis, treatment and follow-up of their clinical condition. The study was conducted in compliance with the terms of the Helsinki II Declaration. Moreover, all parents of children gave their informed consent to the inclusion of their children in the manuscript.

The clinical, biochemical and radiological characteristics of all five patients are summarized in Table 1.

Patient 1

This patient was a female newborn of African origin. She was born at term by vaginal delivery after an uneventful pregnancy. The parents were not related. Apgar score was 8 at the 1st min and 10 at the 5th min. She had no sign of perinatal distress. Birth weight was 2,700 g (−1.23 SD), length 49 cm (−0.22 SD) and cranial circumference 33.2 cm. She did not present evident dysmorphic features. During her first day of life, she presented tremors associated with severe hypoglycemia (21 mg/dL) that did not respond to orally given glucose. She presented respiratory distress that required mechanical ventilation and a septic shock, which at first misled the clinician about etiology of hypoglycemia. The severe hypoglycemia persisted in spite of greater doses of enteral and intravenously glucose (maximum administration of glucose: 8.5 mg/kg/min). The situation persisted even after the resolution of neonatal infection and with normal insulin levels. Moreover, the baby initially presented non-cholestatic jaundice that was treated with phototherapy, but she later developed cholestatic jaundice with increased hepatic cytolytic enzymes. At first, to exclude a metabolic disease, specific tests were performed resulting in evidence of high glycine levels (962 μmol/L, normal range 185–767 μmol/L) with no clear pathologic significance. Endocrinological investigations were done by the 28th day of life, only after the negativity of metabolic investigations. Hormonal levels (specified in Table 1) were evaluated during hypoglycemia and we found severe combined pituitary hormone deficiency. Replacement therapy at beginning with hydrocortisone 25 mg/m^2 then gradually reduced to 20 mg/m^2 three times a day (at 30 days of life), afterwards also with L-thyroxin 25 μg daily (at 33 days of life) resulted in the complete resolution of hypoglycemia and the progressive disappearance of cholestatic jaundice. GH therapy was started later, at 60 days of life. An MRI at 34 days of life allowed us to confirm the diagnosis of congenital hypopituitarism. In particular, the MRI showed aplasia of the anterior pituitary with the absence of PSA and EPP.

Genetic analysis was performed for the HESX1, GLI2 and LHX4 genes, but no mutations have been detected in these genes.

The child is now 1 year old, presents medium mental retardation, maintains good control of her hormonal profile and shows satisfactory growth.

Patient 2

This patient was a male newborn of African origin. He was born at term by vaginal delivery after an uneventful pregnancy. The parents were not related. Apgar score was 10 at the 1st min and 10 at the 5th min. He did not show signs of perinatal distress. Birth weight was 2,670 g (−1.64 SD) and length 49 cm (−0.50 SD). He did not present evident dysmorphic features. He was dismissed from the birth hospital on his third day of life with a weight of 2,570 g and was breastfeeding. That same evening he was brought

Table 1 Clinical, biochemical and radiological characteristics of five patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
MRI phenotype	Adenohypophysis aplasia	Adenohypophysis hypoplasia	Adenohypophysis hypoplasia	Adenohypophysis hypoplasia	Adenohypophysis hypoplasia
	PSA	PSA	PSA, hypoplasia + EPP		PSA
	EPP	EPP	Chiari 1 malformation	EPP	EPP
Presentation of symptoms	Neonatal	Neonatal	Neonatal	Neonatal	Neonatal
Symptoms	Symptomatic neonatal hypoglycemia	Symptomatic neonatal hypoglycemia	Symptomatic neonatal hypoglycemia	Symptomatic neonatal and post-natal hypoglycemia	Symptomatic neonatal and post-natal hypoglycemia
	Respiratory distress	Micropenis	Severe short stature	Severe short stature	Severe short stature
	Septic shock	Cholestatic jaundice	Developmental delay	Neonatal jaundice	Neonatal jaundice
	Cholestatic jaundice				
GH function	Abnormal: GH 2.80 μg/L, IGF1 3.16 nmol/L	Abnormal: GH 2.00 μg/L, IGF1 3.98 nmol/L	Abnormal: GH peak after insulin stimulation 0.10 μg/L, nocturnal GH mean 0.51 μg/L, IGF1 0.39 nmol/L	Abnormal: GH peak after arginine stimulation 0.40 μg/L, GH peak after clonidine stimulation 0.30 μg/L, IGF1 1.83 nmol/L	Abnormal: GH peak after arginine stimulation 1.30 μg/L, GH peak after clonidine stimulation 0.90 μg/L, IGF1 2.37 nmol/L
Cortisol function	Abnormal: cortisol 0.18 μg/dL, ACTH 6.90 pg/mL	Abnormal: cortisol 1.71 μg/dL, ACTH 3.30 pg/mL	Normal: basal cortisol 9.90 μg/dL, cortisol peak after insulin stimulation 30.40 μg/dL, ACTH 12.26 pg/mL	Normal: basal cortisol 13.30 μg/dL, low-dose ACTH stimulated cortisol 25.70 μg/dL, ACTH 16.80 pg/mL	Normal: basal cortisol (during hypoglycemia) 15.1 μg/dL, ACTH 14.65 pg/mL
Thyroid function	Abnormal: TSH 0.03 mU/L (f.d.: 1.82 mU/L), FT4 4.80 pmol/L, FT3 2.10 pmol/L	Normal: TSH 2.52 mU/L, FT4 12.90 pmol/L, FT3 4.00 pmol/L	Normal: TSH 3.72 mU/Lm, FT4 14.90 pmol/L, FT3 5.54 pmol/L	Abnormal: TSH 0.10 mU/L (f.d.: 2.78 mU/L), FT4 7.33 pmol/L	Abnormal: TSH 0.15 mU/L (f.d.: 1.97 mU/L), FT4 9.00 pmol/L
Gonadic function	Apparently normal	Biochemically normal	No investigated	No investigated	No investigated
Posterior pituitary function	Normal	Normal	Normal	Normal	Normal
Therapy	Hydrocortisone (since 30 days)	Hydrocortisone (since 23 days)	GH (since 22 months)	GH (since 8 years)	GH (since 5 years)
	L-thyroxin (since 33 days)	GH (since 52 days)		Hydrocortisone (since 9 years)	L-thyroxin (since 7 years)
	GH (since 60 days)				
Neurologic	Medium mental retardation	Normal	Light developmental delay	Normal	Normal

PSA absence of the pituitary stalk, *EPP* ectopic posterior pituitary, *f.d.* first determination

to the emergency department (ED) of our hospital because he was lethargic and totally refused to eat. In ED, the newborn appeared severely lethargic, with hypotonia and hyporeactivity; his glycemia was 7 mg/dL. Routine glycemic checks showed that asymptomatic hypoglycemia persisted in spite of high doses of enteral and intravenously given glucose. Moreover, on examination, micropenis with normal testis was observed. Endocrinological investigations were performed by the 18th day of life. Hormonal levels were evaluated during hypoglycemia showing insulin in the normal range but there was a deficiency of ACTH, cortisol and GH. Replacement therapy beginning with hydrocortisone 20 mg/m^2 three times a day (at 23 days of life) did not resolve the asymptomatic hypoglycemia. Moreover, the infant presented progressive cholestatic jaundice with an important increase in hepatic enzymes (AST 656 U/L, ALT 300 U/L). Then, metabolic tests were performed with an initial suspect of galactosemia. Therefore, milk feeding was suspended and more specific metabolic tests were run. These tests definitively excluded a metabolic disease and MRI (at 33 days of life) confirmed the endocrinological suspicion of congenital hypopituitarism by revealing adenohypophysis hypoplasia with PSA and EPP. GH therapy was started at 52 days of life with a slight improvement in glycemic control, which was further improved after increasing hydrocortisone doses up to 30 mg/m^2 three times a day. The hepatic alterations persisted (AST 443 U/L, ALT 250 U/L) and allowed us to establish the diagnosis of congenital CMV infection. It was treated with ganciclovir with an improvement of hepatic enzymes.

The child is now 1 year old, presents normal development and growth, with good control of his hormonal profile and an important reduction of hydrocortisone requirements (18 mg/m^2). Thyroid functions are still in the normal range. The micropenis was treated with testosterone 25 mg every 28 days for 3 times with a good increase in the penile size.

Genetic analysis was performed for the HESX1 and LHX4 genes, but no mutations have been detected in these genes.

Patient 3

This patient was a female newborn of Caucasian origin. She was born at term by inducted vaginal delivery after an uneventful pregnancy. The parents were not related. She had no signs of perinatal distress. Birth weight was 2,820 g (−0.98 SD) and birth length 48 cm (−0.78 SD). She did not present evident dysmorphic features. On the second day of life, she presented severe hypoglycemia that responded to intravenous glucose. No specific diagnosis was formulated and the newborn was dismissed from the birth hospital in fifth day of life. At 8 months of life, she was referred for medical attention due to growth impairment. Initial tests excluded malabsorption and did not show evidence of any other disease. At 20 months of life, she presented severe growth retardation with short stature (−5.23 SD), had a language delay and was unable to stand. Endocrine tests showed: GH peak of 0.1 μg/L after insulin stimulation, nocturnal GH mean of 0.5 μg/L, IGF1 0.39 nmol/L, ACTH, cortisol (basal and peak after insulin stimulation) and thyroid function were normal, but she presented a delayed bone age of 16 months. GH therapy was started at 22 months of life and had a good response. After the begin of GH therapy, she was submitted to periodic evaluation of thyroid and adrenal functions; both remained in the normal range.

An MRI, performed at 23 months of life, showed hypoplasia of the anterior pituitary, PSA and hypoplasia and EPP at the level of the floor of the third ventricle. Moreover, she presented a Chiari 1 malformation. Her neurological development was evaluated from pediatric neuropsychiatry which still has in charge of the child. At the moment, a correlation between her developmental delay and the diagnosis of hypopituitarism is not found.

The child is now 4 year old, presents a slight developmental delay, and has satisfactory growth thanks to GH replacement treatment.

Patient 4

This patient was a male newborn of Caucasian origin. He was born at term by Caesarean delivery after an uneventful pregnancy. The parents were not related. He did not show signs of perinatal distress. Birth weight was 4,120 g (1.66 SD), length 53 cm (1.50 SD). He did not present evident dysmorphic features. On the second day of life, he presented generalized seizures associated with severe hypoglycemia (13 mg/dL) that responded to intravenous glucose, which was continued for 4 days. At 3 days of life, he presented jaundice that was treated with phototherapy. No specific diagnosis was formulated and the newborn was dismissed from the birth hospital. There were no other signs or symptoms until 12 months of life, when the baby had another seizure during a respiratory infection with fever and refusal of food. Also in this case, the child was in hypoglycemia (11 mg/dL). Moreover, he presented ketonuria; consequently, he underwent tests to evaluate the cause of hypoglycemia but lactic acid, ammonia, insulin, plasma and urine amino acids, liver function, lipid profile, CPK, cortisol after ACTH test and GH peak after glucagon stimulation were all normal. Later, he had two other episodes of symptomatic hypoglycemia during intercurrent infections, so at 4 year old he was hospitalized in a Pediatric Metabolic Unit to identify a metabolic disease that

had not been confirmed. Nevertheless, the symptomatic hypoglycemia persisted. At 8 years of age, he showed slow growth velocity. In particular, his growth velocity gradually diverged from normal height percentiles presenting short stature and went from 0.8 SD at 2 year old to −1.23 SD at 4 year old, to −2.5 SD at 8 year old. Therefore, he underwent to endocrine tests that showed: GH peak of 0.4 μg/L after arginine stimulation, GH peak of 0.3 μg/L after clonidine stimulation, IGF1 1.83 nmol/L, normal ACTH and cortisol functions (after low-dose ACTH test), and he presented a delayed bone age of 2 years and 6 months. In addition, he presented central hypothyroidism with a TSH that was not consensually increased. MRI showed adenohypophysis hypoplasia and EPP. At 8 years of age, celiac disease was diagnosed and a gluten-free diet was started.

The boy is now 10 year old and shows satisfactory growth thanks to GH replacement treatment, which was begun when he was 8 year old. After the beginning of GH therapy, he was submitted to periodic evaluation of adrenal function that remained in the normal range. Nevertheless, because of persistent symptomatic hypoglycemia during infections, since his ninth year of life he has been treated with hydrocortisone during stress events, with a good response.

Patient 5

This patient was a male newborn of Caucasian origin. He was born at term by vaginal delivery after an uneventful pregnancy. The parents were not related. Apgar score was 9 at the 1st min and 10 at the 5th min. He did not show signs of perinatal distress. Birth weight was 3,600 g (0.48 SD), length 51 cm (0.50 SD) and cranial circumference 36 cm. He did not present evident dysmorphic features. On his first day of life, he had a hypoglycemic crisis that responded to intravenous glucose. At 2 days of life, he presented jaundice that was treated with phototherapy. No specific diagnosis was formulated and the newborn was normally dismissed from the birth hospital. Later on, between 3 and 5 years of age he suffered two other hypoglycemic crises. In these occasions, he was submitted to different tests to evaluate the cause of the hypoglycemia but all metabolic tests resulted normal. Moreover, he was also submitted to the evaluations of thyroid function that resulted normal. Furthermore, he had shown a growth impairment since he was 2 year old. At 5year old, after another episode of hypoglycemia occurred, he was hospitalized in a Pediatric Endocrinology Unit. During hospitalization, it was found that his growth velocity had gradually diverged from normal height percentiles presenting severe short stature (−3.38 DS). Therefore, he underwent to endocrine tests that showed a deficient GH peak after both arginine and clonidine stimulation; very low IGF1, normal ACTH, cortisol (during hypoglycemia) and thyroid functions, and a delayed bone age of 3 years. MRI revealed adenohypophysis hypoplasia, PSA and EPP. During follow-up, he presented central hypothyroidism with a TSH value that was not consensually increased, so replacement therapy with L-thyroxin was started at 7 years of age. The child is now 8 year old, presents normal development and a satisfactory growth thanks to GH replacement treatment, which was started at 5 years of age. After the beginning of GH therapy, he was submitted to periodic evaluation of adrenal function that remained in the normal range.

Discussion

This brief report summarizes the signs and symptoms that permit to diagnose a congenital hypopituitarism with the aim to reduce the time for diagnosis and to be able to begin precocious and appropriate treatment.

In all five cases, the first sign of the disease was early and severe neonatal hypoglycemia that did not respond to glucose administration. In four cases, there was jaundice associated to the hypoglycemia so the clinicians hypothesized a metabolic disease as the first cause of their symptoms and delayed the endocrinological tests. Early diagnosis of hypopituitarism in the neonatal period is difficult because other factors like neonatal infection and respiratory distress can confuse the clinical condition, as for patient 1 [2, 7, 8]. In fact, both birth asphyxia and perinatal stress produce hyperinsulinism as a consequence of the use of anaerobic metabolism to maintain blood glucose concentrations [18]. Therefore, a correct diagnosis of congenital hypopituitarism is made in the neonatal period in only 23 % of cases [19]. Nevertheless, in two out of our five patients with neonatal hypoglycemia, the diagnosis was confirmed by MRI within the 34th day of life, and treatment was started in both cases within the 30th day of life.

Although hypoglycemia represents a common metabolic issue facing both healthy and ill-appearing neonates, if the symptoms persist it is necessary to determine the underlying cause [20, 21]. Neonatal hypoglycaemia that persists or recurs after the first few days of life raises the diagnostic possibility of inborn error of metabolism or of an endocrine disorder. A wide range of rare metabolic disorders can present with neonatal hypoglycaemia, among which: congenital hyperinsulinism, the most severe and frequent form; glyco/gluconeogenesis defects; mitochondrial fatty acid oxidation disorders and some defects in amino acid metabolism. Furthermore, some of these conditions can cause liver failure [22, 23].

On the contrary, hypoglycemia secondary to endocrine deficiencies is uncommon [24] but no less severe, consequently endocrine evaluations are as necessary as metabolic investigations. In fact, recent research has shown a death rate of 1 per 31–54 patients-years in children <6 years of age with a history of hypoglycemia attributable to adrenal insufficiency [25]. Moreover, in England, Canada and USA, 12–25 % of all deaths in children with hypothalamic–pituitary disease were due to hypoglycemia and/or central adrenal insufficiency [26–28]. In our cases, an indication for an endocrine disorder was the presence of jaundice in association with the hypoglycemia. In fact, if one or the other of these symptoms may rarely be involved in the diagnosis of congenital hypopituitarism, when both are present, this diagnosis must be rapidly hypothesized [29]. Indirect hyperbilirubinemia may be caused by thyroxine deficiency that prevents bilirubin conjugation [30]. Cholestasis seems to be due to hypocortisolism because cortisol modulates bile flow and bile acid synthesis. But it has been hypothesized that even GH is also involved in the pathogenesis of this disorder since it seems to modulate the biosynthesis and secretion of biliary acids [7, 31]. From a clinical point of view, the MPHD has to be considered responsible for the liver failure presented in different ways by the patients, as shown by the fact that the hydrocortisone alone does not always resolve the symptomatology, whereas patients often require GH, as for our patient 2 [7, 30]. However, there is no biochemical alteration of hepatic dysfunction that is pathognomonic of congenital hypopituitarism, and in all cases the symptoms regressed with hormone replacement therapy within 6–10 weeks [31–33]. The difficulty in normalizing liver function in case 2 was probably due to the presence of a concomitant CMV infection which complicated the diagnosis and treatment, prolonging recovery. It is known that congenital CMV infections are not very frequent but may cause progressive liver disease, cirrhosis and even death [34].

Another diagnostic difficulty derives from the lack of established hormonal investigations that would help in identifying congenital hypopituitarism in the newborn period [2, 9]. Consensus papers on the diagnosis of GH deficiency (GHD) repeatedly report the lack of an evidence-based approach to the diagnosis of GHD in the newborn. In the neonatal period, the diagnosis can be classically made on the basis of a GH level <20 μg/L during hypoglycemia or after a glucagon stimulation test [35]; but, in the presence of clinical evidence, the diagnosis of severe neonatal GHD can be confirmed during the first week of life by a single randomly taken GH level of less than 7 μg/L [36]. Patients 1 and 2 both presented a basal GH level under 3 μg/L during hypoglycemia, so the diagnosis could already be hypothesized after this blood exam.

In both these cases, the GH treatment was started relatively early, within 2 months of life. This was necessary in patient 2 because the GH therapy was essential in maintaining the glycemia in the normal range. Moreover, literature suggests that in suspected cases of neonatal GHD, independently from neonatal symptoms, GH therapy should be started immediately [36]. It is known, in fact, that if children with congenital hypopituitarism are usually of normal or moderately reduced size and weight at birth, there is a rapid growth impairment in the first months of life [5]. Consequently, children with untreated GHD are often more than 4 SD below the mean by 1 year of age and achieve only 70 % of their full growth potential. As a consequence, they present a deficit on average of 38 cm in males and 33 cm in females. This data emphasize the importance of early diagnosis and treatment, before the statural impairment becomes particularly evident [16]. Thanks to early GH treatment, children with hypopituitarism present a mean gap between final size and parental target size of only 0.1 ± 1.1 SD, confirming, therefore, that early diagnosis and treatment are essential in this setting [37].

After the beginning of GH treatment, particular attention has to be paid to thyroid and cortisol function. Some patients, in fact, develop either primary or central hypothyroidism while treated with GH. Similarly, there is a risk of developing adrenal insufficiency that, if unrecognized, can be fatal. Periodic evaluation of thyroid and adrenal function is therefore indicated for all patients treated with GH [16].

Thyroid function was assessed and revealed central hypothyroidism in patients 1, 4 and 5: all of them at first investigation presented low FT4 with a TSH not consensually increased. This is not an innovative result because other authors have described this phenomenon as probably due to the presence of some thyrotropin-producing cells [7, 38, 39]. On the contrary, patients 2 and 3 still have normal thyroid function.

In both, patients 1 and 2, we started replacement therapy with hydrocortisone as soon as possible to avoid the severe hypoglycemia that occurred in the first days of life. We used a high dose of hydrocortisone to prevent hypoglycemia, in particular in patient 2 who also needed GH treatment to normalize his glycemia. In both, the doses were progressively reduced. The use of large doses of a fat-soluble hormone as hydrocortisone has been previously described during cholestasis because in this condition, there is an insufficiency of bile acids secretion in the intestine and consequently, a difficulty for the absorption of fat-soluble substances [40].

Patient 2, also, presented a micropenis that was recognized only at the readmission to the hospital because of a severe hypoglycemia. Micropenis may often be the first

clinical sign to suspect a congenital hypopituitarism, as in this case. In utero, in fact, penis growth is consequent to androgens produced by fetal pituitary gonadotropins; consequently, micropenis in a newborn often suggests a defect in some component of the hypothalamic–pituitary–gonadal axis during fetal development. Therefore, it is essential that it is recognized as quickly as possible so that an appropriate treatment can be started to minimize medical and psychological complications [41]. About the therapy of micropenis in congenital hypopituitarism, there are different positions: some authors reported that a considerable growth of the penile size may be obtained with GH replacement therapy, indirectly emphasizing the importance of precociously starting GH therapy [42]; others underline the necessity of testosterone administration to increase the penis size [7, 43]. Finally, some authors have recently suggested that the use of recombinant human FSH and LH injections during the neonatal period showed encouraging results in improving sexual and reproductive functions in adulthood [44].

In three of our cases, the diagnosis was made after the neonatal period, respectively, at 2, 8 and 5 years of life. In all patients, the hypoglycemic symptoms present at birth were not appropriately investigated and later on for patients 4 and 5, the metabolic investigations were preferred to endocrinological tests. Therefore, the definitive diagnosis was delayed. In all three cases, the main clinical sign was severe growth impairment. These different clinical presentations of the same condition underline that hypopituitary phenotypes can be highly variable and can evolve over time [2]. In this contest, it is necessary to evaluate the pituitary–adrenal function. In fact, it is described that patients with GHD and EPP, as all these three children, developed a central adrenal insufficiency within 2 years of follow-up [45]. If an overt adrenal failure is easily discernible, the detection of asymptomatic children with a subtle dysfunction of the pituitary–adrenal axis is still a difficult diagnosis. Nowadays, the reference test for the diagnosis is considered the insulin tolerance test [46] that was performed in patient 3. Nevertheless, recent data identified the low-dose ACTH test as useful in the study of the integrity of the pituitary–adrenal axis in children older than 3 years. Moreover, the usefulness of this test should be higher than the standard dose ACTH test, for this group of children [46]. Because patient 4 was submitted to GH stimulating tests in another hospital where the insulin tolerance test was not used, we preferred to use the low-dose ACTH test to evaluate the pituitary–adrenal function. On the contrary, for patient 5, the normality of ACTH and cortisol during hypoglycemia allowed us to avoid the stimulating test, for the evaluation of adrenal–pituitary axis.

The diagnosis was definitively confirmed in all cases by MRI. MRI patterns have important clinical interpretation for both treatment and follow-up. In fact, in one study after a mean follow-up period of 4.5 years, 5.4 % of subjects with isolated GHD and abnormal MRI progressed to MPHD, while none of those with normal MRI progressed [47]. Moreover, the identification of a particular MRI phenotype is also helpful in terms of genetic counselling, though none of our patients present, at the moment, confirmed genetic alteration as the cause of their MRI phenotype [8, 10]. Since the evolution of the disease can possibly involve other pituitary hormone deficiencies over time, genetic analysis should also be taken into account for the future follow-up of these patients, including other candidate genes [15–17].

A correlation between EPP and stalk abnormality and MPHD has been described; these patients in particular have shown GHD, hypocortisolism and hypothyroidism [47]. Whereas patient 1 had alterations of all three axes, patient 2 presented only the alteration of the GH and cortisol axes and patients 4 and 5 only of the GH and thyroid axes. They are again, most likely, too young to present the other hormone deficiencies and a strict, lifelong follow-up will be necessary to evaluate their clinical evolution. In fact, as mentioned above, the clinical presentation of pituitary hormone disease may be dynamic because subsequent additional hormone deficiencies may develop over time [48].

In conclusion, the clinical phenotype of congenital hypopituitarism is highly variable and consequently the definitive diagnosis is often delayed. In fact, in four out of five our cases, the clinical signs suggested a metabolic disorder which initially misled the clinician regarding the etiology of the children's clinical condition. We would like to emphasize the importance of suspecting congenital hypopituitarism in the presence of severe and persistent neonatal hypoglycemia associated with cholestatic jaundice and in childhood in the presence of a precocious reduction of growth velocity that gradually diverges from normal height percentiles presenting severe short stature.

In all such cases, it is necessary to carry out as soon as possible the investigations necessary for the diagnosis, in particular a hypothalamic–pituitary MRI scan, and finally to start the appropriate treatment as soon as possible.

Conflict of interest The authors declare that there is no conflict of interest that could compromise the impartiality of the research reported and that for this study no financial supports were requested.

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