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Long-term follow-up of patients with Bartter syndrome type I and II

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Abstract

Background. Little information is available on a long-term follow-up in Bartter syndrome type I and II.

Methods. Clinical presentation, treatment and long-term follow-up (5.0–21, median 11 years) were evaluated in 15 Italian patients with homozygous ($n = 7$) or compound heterozygous ($n = 8$) mutations in the *SLC12A1* ($n = 10$) or *KCNJ1* ($n = 5$) genes.

Results. Thirteen new mutations were identified. The 15 children were born pre-term with a normal for gestational age body weight. Medical treatment at the last follow-up control included supplementation with potassium in 13, non-steroidal anti-inflammatory agents in 12 and gastroprotective drugs in five patients. At last follow-up, body weight and height were within normal ranges in the patients. Glomerular filtration rate was <90 mL/min/1.73 m^2 in four patients (one of them with a pathologically increased urinary protein excretion). In three patients, abdominal ultrasound detected gallstones. The group of patients with antenatal Bartter syndrome had a lower renin ratio ($P < 0.05$) and a higher standard deviation score (SDS) for height ($P < 0.05$) than a previously studied group of patients with classical Bartter syndrome.

Conclusions. Patients with Bartter syndrome type I and II tend to present a satisfactory prognosis after a median follow-up of more than 10 years. Gallstones might represent a new complication of antenatal Bartter syndrome.

Keywords: Bartter syndrome; cholelithiasis; growth retardation; *KCNJ1* gene; *SLC12A1* gene

Introduction

Bartter syndrome type I (BS I) and type II (BS II) are salt-wasting renal tubular disorders that are clinically characterized by polyhydramnios leading to premature delivery, marked polyuria and a tendency towards nephrocalcinosis [1,2]. Loss-of-function mutations either in the furosemide-sensitive sodium–potassium–chloride cotransporter gene (*SLC12A1*; BS I, OMIM 601678) or in the inwardly rectifying potassium channel ROMK gene (*KCNJ1*; BS II, OMIM 241200) have been identified in the vast majority of patients with this autosomal recessive disorder [3,4]. Mutations in the CLCNKB chloride channel gene (Bartter syndrome type III also defined as classical Bartter syndrome—OMIM 607364) as well as in the BSND gene (Bartter syndrome form associated with sensorineural deafness—Bartter type IV—OMIM 602522) are also sometimes responsible for an identical clinical phenotype but will not be treated in this report.

Little information is currently available on the disease course of these patients [5–7]. The purpose of the current analysis was to shed additional light on clinical presentation, initial diagnostic pitfalls and especially follow-up in 15 patients with bi-allelic mutations either in the *SLC12A1* or in the *KCNJ1* genes. The outcome in patients with antenatal Bartter syndrome was also compared with that observed in a recently published group of patients affected with classical Bartter syndrome [8].

Materials and methods

Among 34 patients with the clinical and biochemical diagnosis of antenatal Bartter syndrome on follow-up at our institutions, 15 presented homozygous or compound heterozygous mutations in the *SLC12A1* or *KCNJ1* genes together with a clinical–biochemical follow-up of 5 years or more. Thirteen patients with antenatal Bartter syndrome presenting bi-allelic mutations and a shorter follow-up and another six patients with only one mutation detected were not further analysed in this study. The clinical features at presentation and at the last follow-up control were collected for these patients. The glomerular filtration rate was estimated from height and creatinine using the original Schwartz formula [9]. Since plasma renin (or plasma renin activity) and aldosterone were evaluated in different laboratories, we refer to their results either as renin ratio or aldosterone ratio. These indexes were calculated by dividing the individual renin (either plasma renin activity or active renin level) or aldosterone value by the corresponding upper reference value [8]. Renal ultrasound imaging was performed at diagnosis and at last follow-up in all patients. The last renal ecography was also evaluated for the grade of medullary nephrocalcinosis by three different paediatricians. The grading scale for medullary nephrocalcinosis was as follows: grade 1, mild increase in the echogenicity around the border of the medullary pyramid; grade 2, mild diffuse increase in the echogenicity of the entire medullary pyramid; grade 3, greater or more homogeneous increase in the echogenicity of the entire medullary pyramid. In some patients, follow-up imaging included also the evaluation of liver and gallbladder.

The non-parametric two-tailed Mann–Whitney–Wilcoxon test for two independent samples was used for analysis. Statistical significance was defined as a P-value of <0.05.

Genomic DNA was extracted from peripheral white blood cells using standard methods. All coding sequences of *SLC12A1* and *KCNJ1* genes with their intron/exon boundaries were amplified by means of PCR using specific primer pairs. Direct sequencing of the purified PCR products was then performed bidirectionally by the dye terminator cycle sequencing method (Applied Biosystem, Foster City, CA, USA) loaded on a 16-capillary ABI Prism 3100 genetic analyser (Applied Biosystem, Foster City, CA, USA) and analysed with the Sequencing Analysis 3.7 software. Mutations were discerned from polymorphisms by demonstration of their absence in 100 control chromosomes. The nomenclature is based on the recommendations of the Human Genomic Variant Society starting with the nucleotide 1 of the start codon (ATG) at cDNA level. A written informed consent had been obtained from all patients and their family members.

Results

Molecular findings

The 15 patients with homozygous or compound heterozygous mutations considered in this study (8 female and 7 male subjects) belong to 15 non-consanguineous Italian families (Table 1). The results of direct sequencing of the *SLC12A1* and *KCNJ1* genes revealed 13 new mutations and 7 previously described mutations. Patient 3, who carried a compound heterozygous mutation, had been previously described as a single heterozygous mutation [10]. Among the 10 patients presenting *SLC12A1* gene

Table 1. Molecular characterization of the genetic defects in the *SLC12A1* (Bartter syndrome type I) or *KCNJ1* (Bartter syndrome type II) genes

| Patient number	Gender	Bartter syndrome type	Status	Nucleotide change	Predicted effect on protein	Exon	Type of mutation	Reference
1	Female	I	Homozygous	c.1381T>C	p.[Cys461Arg] + [Cys461Arg]	10	Missense	[10]
2	Male	I	Homozygous	c.1062delG	p.[Lys354AsnfsX73] + [Lys354AsnfsX73]	7	Frameshift	[10]
3	Female	I	Compound heterozygous	c.1381T>C / c.1630C>T	p.[Cys461Arg] + [Pro544Ser]	10/12	Missense / missense	[10] / new
4	Male	I	Compound heterozygous	c.347G>A / c.1954G>A	p.[Arg116His] + [Gly652Ser]	1/15	Missense / missense	New / new
5	Female	I	Homozygous	c.903_904delC	p.[Arg302GlyfsX2] + [Arg302GlyfsX2]	6	Frameshift	[3]
6	Female	I	Homozygous	c.1663G>A	p.[Ala555Thr] + [Ala555Thr]	12	Missense	[10]
7	Male	I	Compound heterozygous	c.551T>A / c.611T>C	p.[Leu184Gln] + [Val204Ala]	2/3	Missense / missense	New / new
8	Female	I	Compound heterozygous	c.1190G>C / c.3164+1G>A	p.[Gly397Ala] + c.[3164+1g>a]	8/25	Missense / splice site	New / [7]
9	Male	I	Compound heterozygous	c.1493C>T / c.1522G>A	p.[Ala498Val] + [Ala508Thr]	11/11	Missense / missense	New / [19]
10	Female	I	Compound heterozygous	c.903_904delC / c.1493C>T	p.[Arg302GlyfsX2] + [Ala498Val]	6/11	Frameshift / missense	[3] / new
11	Female	II	Compound heterozygous	c.808C>T / c.592G>T	p.[His270Thr]+ [Ala198Ser]	5	Missense / missense	New / new
12	Female	II	Compound heterozygous	c.80G>A / c.277T>G	p.[Trp27X] + [Phe93Val]	5	Nonsense / missense	New / new
13	Male	II	Homozygous	c.572C>T	p.[Thr191Ile] + [Thr191Ile]	5	Missense	New
14	Male	II	Homozygous	c.808C>T	p.[His270Thr] + [His270Thr]	5	Missense	New
15	Male	II	Homozygous	c.422C>T	p.[Thr141Ile] + [Thr141Ile]	5	Missense	New
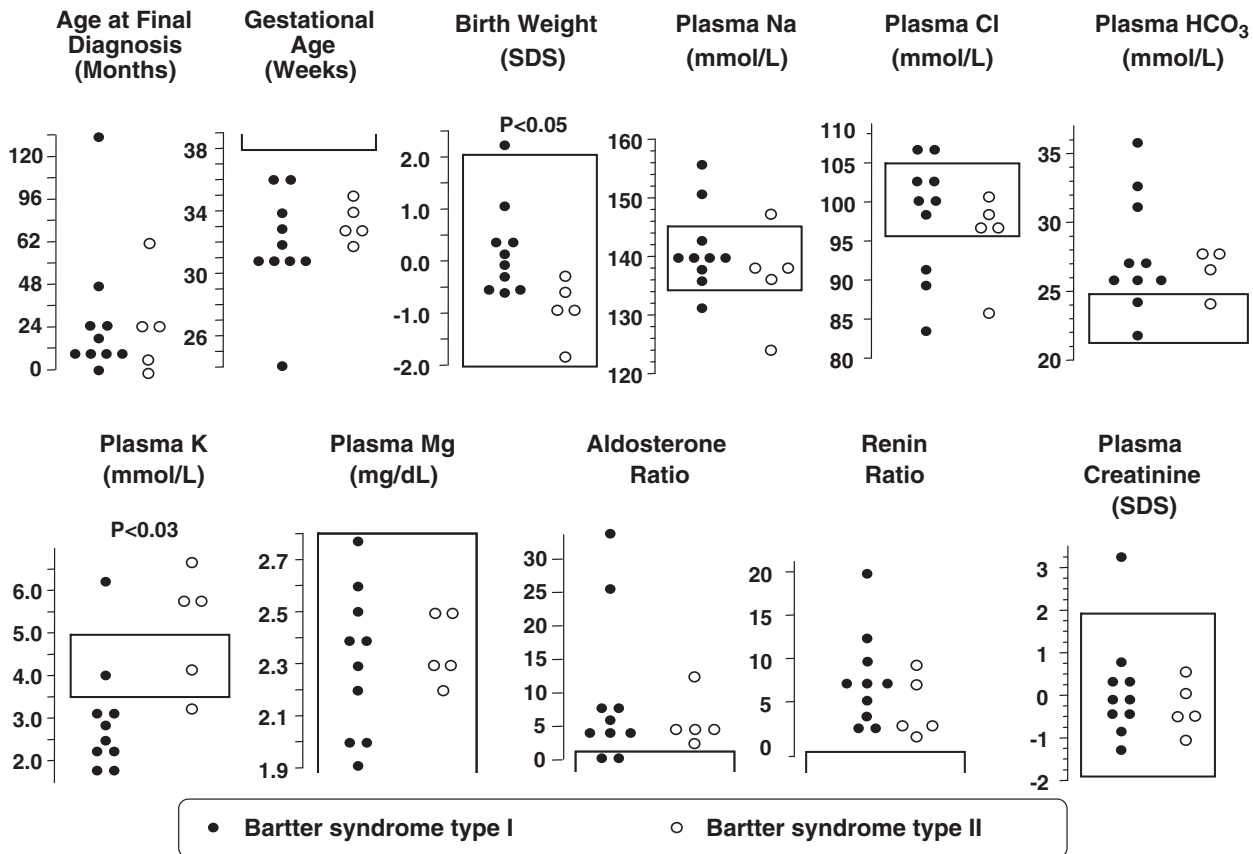
Fig. 1. Age at the final diagnosis and the initial clinical and laboratory data in 15 patients with homozygous or heterozygous mutations in the *SLC12A1* (BS I; closed symbols) or *KCNJ1* (BS II; open symbols) genes. Plasma bicarbonate was not assessed at presentation in one patient affected with BS II. Birth weight SDS was significantly higher (P < 0.05) and plasma potassium lower (P < 0.03) in BS I than in BS II. The frames denote the reference ranges.

mutations, 6 were compound heterozygous and 4 homozygous. Among the five patients presenting *KCNJ1* gene mutations, three were homozygous and two compound heterozygous. The homozygous mutations were confirmed on both the parents of the patients in order to exclude the presence of a heterozygous deletion of corresponding exons. The genetic abnormalities described were not present in a sample of 50 healthy controls (100 chromosomes investigated).

Initial findings

History of premature delivery, polyhydramnios and polyuria was present in all patients, but the final clinical diagnosis of Bartter syndrome was made before the age of 26 months in 12 patients (Figure 1). Birth weight was never less than 2 standard deviation scores (SDS) below the mean for gestational age. The birth weight SDS was on the average higher (P < 0.05) in BS I than in BS II patients. The diagnosis of diabetes insipidus was initially suspected in two BS I patients who presented with hypernatraemia and that of pseudohypoaldosteronism in the two BS I patients who presented with plasma potassium >6.0 mmol/L. In one of them (Patient 7), acute renal failure was also present.

The overall median plasma sodium was 137 mmol/L (range 125–156), and it was increased in three and mildly

decreased in two patients (Figure 1). The overall median plasma chloride was 98 mmol/L (range 84–107), and it was decreased in four patients. Plasma potassium was reduced in eight but normal (*n* = 1) or even increased (*n* = 1) in BS I patients (median 2.7, range 1.9–6.3 mmol/L). On the contrary, the level of this electrolyte was mildly reduced in one but normal (*n* = 1) or even increased (*n* = 3) in four of the five BS II patients (median 5.7, range 3.3–6.7 mmol/L): the difference between BS I and BS II was significant (P < 0.03). Hyperbicarbonataemia (HCO_3^- >25 mmol/L) was similarly frequent both in patients with BS I (8 of 10 patients) as well as in patients with BS II. The overall median plasma bicarbonate was 27 mmol/L (range 25–32). No hypomagnesaemia was noted in the 15 patients, and the overall median plasma magnesium level was 2.4 mg/dL (range 1.9–2.8). Aldosterone ratio was increased in all but two patients, and renin ratio was increased in all patients. Plasma creatinine was moderately increased in 1 of the neonates affected with Bartter type I syndrome (Patient 7) and normal in the remaining 14 patients (Figure 1).

Renal ultrasound disclosed signs of medullary nephrocalcinosis in all patients with the exception of one BS II patient (Patient 11). The degree of nephrocalcinosis at diagnosis and the urinary calcium excretion were not evaluated.

Follow-up

Clinical and biochemical data at the last follow-up are given in Figure 2. None of the 15 patients suffered from overt underweight or small stature. Plasma sodium and chloride were within the normal ranges in all patients with the exception of one BS I patient who presented with mild hypochloraemia. The overall median plasma sodium was 139 mmol/L (range 137–145) and plasma chloride 101 mmol/L (range 93–108), respectively. Plasma potassium was reduced in 6 of the 10 BS I patients (median 3.1, range 2.5–4.3 mmol/L) and within the normal ranges in all BS II patients (median 3.9, range 3.6–4.1 mmol/L). However, the difference in plasma potassium between these two groups did not reach significant values. Hyperbicarbonataemia was noted in 9 of the 10 BS I patients (median 27, range 25–31 mmol/L) and in 2 of the 5 BS II patients (median 25, range 24–26 mmol/L). The plasma total magnesium level was never reduced in the 15 patients. Aldosterone ratio was normalized in seven patients: four with BS I and three with BS II. Renin ratio was normalized in four patients. Glomerular filtration rate was >90 mL/min/1.73 m^2 in 11 and mildly reduced in 4 patients, 2 patients each with BS I and BS II. Moderate glomerular proteinuria (~1 g/day) was noted in one of the patients with a reduced glomerular filtration rate (Patient 5).

The urinary molar calcium/creatinine ratio was evaluated at the last clinical control in 8 out the 10 patients with BS I and in 3 out of 5 patients with BS II: this parameter was increased (>0.60) in 10 of the 11 aforementioned patients.

As at presentation, renal ultrasound disclosed signs of nephrocalcinosis in all patients with the exception of Patient 11. Nephrocalcinosis was classified as follows: five BS I patients presented with grade 2 and five with grade 3; 2 BS II patients presented with grade 1 and two with grade 3. At least one complete abdominal ultrasound was performed in 10 patients: in three patients, two with BS I (Patient 8 and 9) and one with BS II (Patient 13), asymptomatic gallstones were detected (1–3 stones per patient with a diameter of ≤5 mm). Long-term parenteral nutrition, a recognized cause of gallstones, had been performed in Patient 8. The age at detection of cholelithiasis was 2.2 and 8.7 years in BS I and 2.9 years in BS II. A persistent cholelithiasis was demonstrated on follow-up in Patient 9 and 13. No corresponding follow-up is so far available for Patient 8.

All patients had normal blood pressure, and no hearing loss during the follow-up period was detected. The neurodevelopmental assessment was normal in the patients with the exception of Patient 15 who presented a mild left hemiparesis secondary to neonatal ischaemic brain damage.
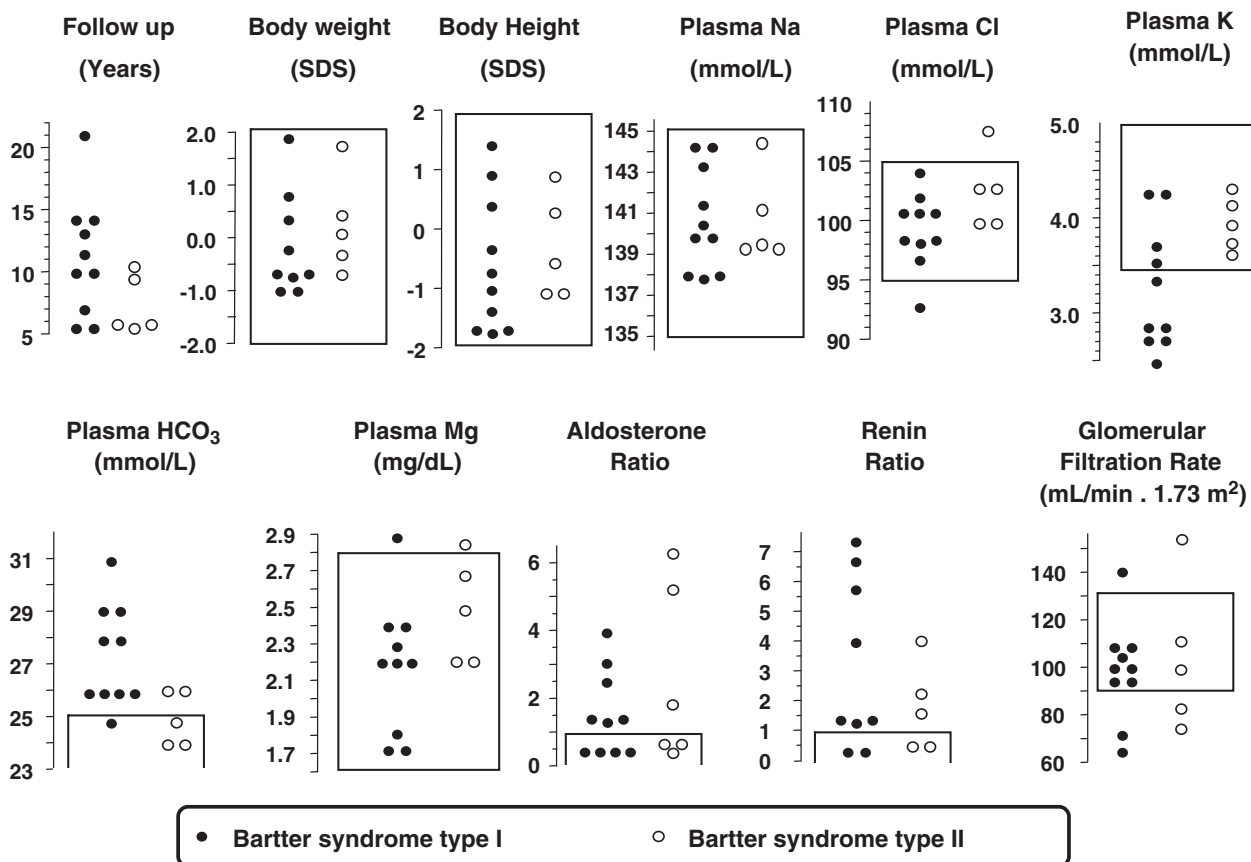

Fig. 2. Clinical and laboratory features in 15 patients with homozygous or heterozygous mutations in *SLC12A1* (BS I; closed symbols) or in *KCNJ1* (BS II; open symbols) genes 5.0–21, median 11 years after diagnosis. No significant difference was noted between BS I and BS II syndromes. The frames denote the reference ranges.
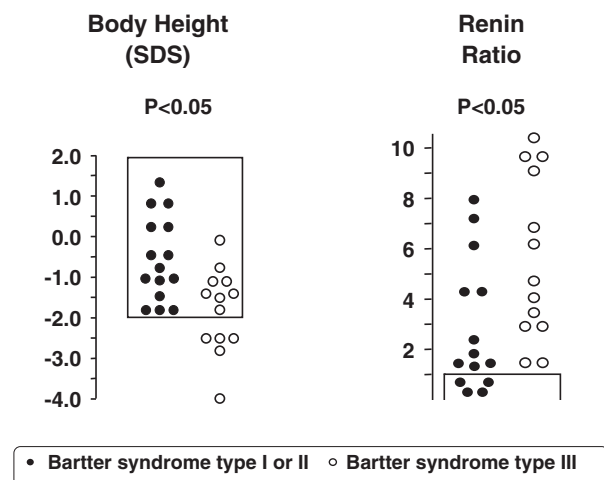
Body Height (SDS)

P<0.05

Renin Ratio

P<0.05

● Bartter syndrome type I or II   ○ Bartter syndrome type III

Fig. 3. Body height SDS and renin ratio in 15 patients with BS I or BS II (closed symbols) 5.0–21, median 11 years after diagnosis, and in 13 patients affected with BS III (open symbols) 5.0–24, median 14 years after diagnosis [8]. Height SDS was significantly higher ($P < 0.05$) and plasma renin ratio lower ($P < 0.05$) in BS I and BS II syndromes than in BS III. The frames denote the reference ranges.

Medical treatment at the last follow-up control included the non-steroidal anti-inflammatory agent indomethacin in 11 patients (from 0.2 to 2.2, median 0.9 mg/kg body weight daily), flurbiprofen in one patient, gastroprotective agents in five patients (ranitidine, $n = 4$; lansoprazole, $n = 1$) and spironolactone associated with hydrochlorothiazide in one patient. Supplementation with potassium chloride was administered in 13 patients (from 0.5 to 2.3 mmol/kg body weight daily). Patient 3 developed a peptic ulcer at 6 years of age on indomethacin 2.0 mg/kg body weight daily. This agent was reintroduced 2 years later without recurrence of the peptic disease. In Patient 2, a growth hormone deficiency was demonstrated on follow-up, and treatment with recombinant human growth hormone was introduced during 3 years.

Comparison with classical Bartter syndrome (BS III)

The findings at follow-up in our 15 patients with BS I and BS II were compared with those noted in a group of 13 patients affected with BS III recently as reported by some members of our group [8]. No differences between the two groups were noted with respect to the blood levels of sodium, potassium, chloride and bicarbonate; the aldosterone ratio; and the glomerular filtration rate. The plasma renin ratio was significantly ($P < 0.05$) lower in the group of patients with BS I and BS II as compared with BS III (Figure 3). The height SDS was significantly ($P < 0.05$) higher in BS I–II types than in BS III. No significant correlation between renin ratio and height SDS was noted in BS III, in BS I–II types or in the cumulated group of patients with either BS III or BS I–II types.

Discussion

The present study describes the genetic findings, the initial clinical and laboratory characteristics, and especially, the

outcome and current management in 15 patients with homozygous or compound heterozygous mutations in the *SLC12A1* and *KCNJ1* genes after a median follow-up of 11 years. BS I patients showed mutations that were spread all over the *SLC12A1* gene; on the contrary, all BS II patients showed mutations in exon 5 of the *KCNJI* gene, as mainly observed [3–7]. The seven new mutations in the *SLC12A1* and five out of the six mutations in the *KCNJ1* were missense. The 13 new missense variants are likely pathogenic, since they substitute highly conserved amino acids in both the genes and were not detected in 100 healthy chromosomes.

The p.Arg116His mutation identified in Patient 4, which has also been described as a single-nucleotide polymorphism (rs34819316), was detected in another homozygous patient not included in this study. So far, functional studies have never been performed on this variant unequivocally demonstrating its polymorphic nature.

It is assumed that patients affected by antenatal Bartter syndrome are often born prematurely or with a small for gestational age birth weight [5–7]. The present survey confirms that these patients are born prematurely after a pregnancy complicated by polyhydramnios but with a normal for gestational age weight, therefore excluding major intrauterine growth retardation in these conditions (however, the birth weight SDS is lower in BS II than in BS I patients). Patients with BS I and BS II present with similar clinical and laboratory findings with the exception of potassium level, which is often reduced in BS I but normal or even increased in BS II [5–7].

Since hypokalaemia and metabolic alkalosis, two peculiar biochemical findings in Bartter syndrome, are often absent at presentation in the antenatal form of this syndrome, other conditions including diabetes insipidus (in subjects with hypernatraemia) or pseudohypoaldosteronism (in patients with hyperkalaemia) are initially suspected in some cases [5,7,11].

Patients with antenatal Bartter syndrome are managed with potassium chloride and non-steroidal anti-inflammatory agents, mostly indomethacin. The present experience confirms that, in patients affected by hypokalaemic salt-losing tubulopathies, gastrointestinal side effects of non-steroidal anti-inflammatory agents are rather rare and not severe [5,8,12]. This observation is likely related to the lower dose of indomethacin (on average 0.9 mg/kg/body weight daily) as compared with other studies [5,7,12]. Obviously, the risks associated with a suboptimal correction of hypokalaemia must be balance against the risks of high-dose therapy with indomethacin.

In our antenatal Bartter patients, both the neurodevelopmental outcome and the somatic growth are almost always normal. In salt-wasting renal tubular disorders, somatic growth retardation is common and traditionally causally linked among others with extracellular fluid volume depletion [13]. The present data with a better growth in BS I and BS II than in BS III and with a higher renin ratio, a recognized marker of fluid volume depletion, in BS III than in BS I and BSII support the aforementioned link between growth retardation and fluid volume depletion in the various forms of Bartter syndrome. Potassium deficiency may also impair the metabolism of growth hormone [14]; however, the sim-

ilar potassium level in antenatal and in classical Bartter syndrome may suggest that potassium does not account for growth retardation in classical Bartter syndrome.

A glomerular filtration rate of <90 mL/min/1.73 m^2, sometimes associated with overt proteinuria, was noted on follow-up in approximately one quarter of our patients. Nephrocalcinosis is a possible explanation for these observations. Prolonged hypokalaemia, which can lead to interstitial fibrosis and tubular atrophy, is a further possible cause [15]. Finally, non-steroidal anti-inflammatory agents have also been associated with reduced renal function [16]. However, in antenatal Bartter syndrome, the use of indomethacin is not related to any relevant lesion on renal biopsy [5].

We were surprised by the fact that three patients with antenatal Bartter syndrome developed gallstones, confirming a recent case report [17]. Possible explanations are that these patients are born prematurely, that they present with laboratory characteristics, which may be mimicked by medication with loop diuretics, and that both prematurity and long-term administration of loop diuretics predispose to gallbladder stone formation in childhood [18]. Alternatively, in these patients, the process of gallstone formation might result from an altered function of either the sodium–potassium–chloride cotransporter or the channel ROMK within the hepatobiliary system.

In conclusion, our patients with homozygous or compound heterozygous mutations in the *SLC12A1* or *KCNJ1* genes managed with potassium chloride and indomethacin present a satisfactory somatic growth after a median follow-up of 11 years. Some impairment of kidney function is observed in approximately one quarter of the patients. Finally, a large subset of these patients develops gallbladder stones.

Conflict of interest statement. None declared.

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