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Hypokalemic nephropathy in an adult patient with partial empty sella: a classic Bartter's syndrome, a Gitelman's syndrome or both?

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Bartter's syndrome belongs to a group of hypokalemic renal channel diseases. These channels are located in the lipid layer of cell membranes where they exist as water channels through which ion transport is performed. Based on the type of genetic disorder and clinical presentation, Bartter's syndrome is classified as neonatal, classical and Gitelman's syndrome. Most of the cases have been noted in pediatric age groups and adult-onset cases are very rare. Moreover, an association between Bartter's syndrome and empty sella has recently been reported in 3 children. We report here the second case of an adult patient affected by Bartter's syndrome with partial empty sella. The patient showed some clinical and histological characteristics of both classic Bartter's syndrome and Gitelman's syndrome, suggesting that genotype and phenotype of Bartter's syndrome are not so clear-cut and that phenotypic overlap may occur, according to a recent hypothesis. Magnetic resonance imaging disclosed a partial empty sella. A thorough endocrinological investigation showed normal hypophyseal, thyroidal, adrenal and gonadal function. Good therapeutic effects were achieved using spironolactone, ACE-inhibitor and potassium supplementation, with normalization of the kalemia. At present, the value of the association of Bartter's syndrome and empty sella remains unclear and future studies are needed to clarify the importance of this association, both in children and in adult patients affected by Bartter's syndrome.

KEY WORDS: Bartter's syndrome - Gitelman's syndrome - Hypokalemic nephropathy - Empty sella.

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Bartter's syndrome belongs to a group of hypokalemic renal channel diseases caused by a molecular hereditary disorder of ion channels in renal tubules. These channels are located in the lipid layer of cell membranes where they exist as water channels through which ion transport is performed. Based on the type of genetic disorder and clinical presentation, Bartter's syndrome is classified as neonatal, classic and Gitelman's syndrome.[1]

Antenatal Bartter's syndrome with hypercalciuria and nephrocalcinosis or hyperprostaglandin E syndrome is a severe form, often revealed by hydramnios, prematurity and growth delay. It is related to a mutation of 2 types of genes encoding for transporters of Henle's loop: the bumetanide-sensitive cotransporter Na-K-2Cl (NKCC2) or the inwardly-rectifying potassium channel (ROMK).[2]

The classical form or type III Bartter's syndrome, often revealed by dehydration in the first year of life, is associated with hypomagnesemia in 20% of cases and normal or increased calciuria. This form is related to mutations of the CLCNKB gene encoding for a chloride channel in Henle's loop.[2]

Gitelman's syndrome or hypocalciuria-hypomagnesemia syndrome is a mild form often discovered in childhood or teenagers in reason of tetany. It is a homo-

geneous disorder related to mutations of the genes encoding the thiazide-sensitive Na-Cl cotransporter located in the distal convoluted tubule.[3]

Recently, 2 additional genes that function as regulators of salt transporters have been shown to cause Bartter's syndrome. Even with these new findings, probably not all of the Bartter-causing genes have been identified.[4]

Most of the cases have been noted in the pediatric age group and adult-onset cases are very rare. In the few cases described in adult subjects, the reasons for late onset are still unclear.[5]

Moreover, an association between Bartter's syndrome and empty sella has recently been reported in a child affected by antenatal Bartter's syndrome [6] and in 2 children [7] affected by Gitelman's syndrome; this association in an adult patient affected by Bartter's syndrome has only been described by Colussi *et al.* in 1992.[8]

We report clinical and laboratory data of an adult patient with some characteristics of both classical Bartter's syndrome and of Gitelman's syndrome and partial empty sella. At present, the importance of this association remains unclear.

Case report

On 28th June 2003, C.B., a 28-year-old man, was admitted to the Emergency Department of another hospital presenting general malaise, fatigue and reported a decreased level of activity, abdominal pain, palpitation of the heart, nausea and vomiting, intense sweating, headache, associated with oliguria. Laboratory findings showed low serum potassium (2.8 mEq/L) and sodium (128 mEq/L), increased creatinine level (1.9 mg/dL), high urea nitrogen (122 mg/dL), with normal serum calcium and magnesium. Blood pressure was 120/70 mmHg. Arterial blood gas showed mild metabolic alkalosis. Urinalysis was normal. Abdominal and renal ultrasonography was unrevealing. For these reasons he was admitted to the Department of Internal Medicine of the same hospital. Acute prerenal renal failure was diagnosed and the patient was treated with a rehydrating solution. Serum electrolyte levels were measured after treatment and they turned out to be normal. During hospitalization the symptoms gradually resolved and after 7 days (5th July) the patient was discharged normohydrated without vomiting or other symptoms related to electrolyte disturbances.

One month later, on 20th July, C.B. began to observe increasing, persistent and diffuse muscle weakness with diffuse cramps. Because of the recurrence of these symptoms and the reappearance of nausea and vomiting, he was admitted to the Emergency Department of our Hospital on 28th July, with the additional symptoms of headache, epigastric pain and lumbodynia; he experienced 2 episodes of confusion. Laboratory tests showed hypokalaemia (3.2 mEq/L), hyponatraemia (112 mEq/L) with normal magnesemia, serum creatinine of 1.6 mg/dL and blood urea nitrogen of 130 mg/dL. Arterial blood gas levels revealed pH 7.887, PCO_2 14.9 mm/Hg, HCO3- 30.5 mmol/L, base excess +13 mmol/L. Suspecting an acute prerenal renal failure, the patient was parenterally rehydrated and was then sent to our Department of Internal Medicine where he was re-evaluated. On admission, physical examination was unremarkable and no significant alteration in the abdominal, heart and lungs was found on inspection. From a neurological point of view the patient was fully oriented, and the cranial-nerve functions were intact. Manual muscle tests revealed light weakness in his extremities. Sensation was normal in all modalities. Deep tendon reflexes were present. The patient showed excessive perspiration, he had a normal body temperature and blood pressure (120/80 mmHg). He reported the persistence of polyuria (about 4 000 cc/day) which started 3 or 4 days before being admitted to the hospital.

Despite the treatment, the hypokalemia gradually exacerbated (2.8 mEq/L), while there was a progressive normalization of the other biochemical data. Metabolic alkalosis was still present.

Urine had pH 6.0 and specific gravity 1.004, no glucose, protein, blood, or ketones were present, urinary calcium (21 mg/L), potassium (16 mEq/L), sodium (3 mEq/L) and chloride (7 mEq/L) levels were low. Urineculture was sterile. Creatinine clearance was normal (90 mL/min). Microalbuminuria was absent.

Renal parenchymal volume and mean renal length, calculated by ultrasonography, were normal; no obstructive uropathy was observed; the echo-Doppler did not show the presence of renal artery stenosis. Renal angio-scintigraphy was performed and it showed normal perfusion of the renal parenchyma. Plain computed tomography was unrevealing.

Possible causes of hypokalemia, such as surreptitious diuretic and laxative abuse, persistent vomiting and diarrhoea, hypomagnesemia [9] and salmonella infection [10] were excluded.[11]

To investigate the abdominal pain, associated with transient nausea and vomiting, the patient underwent an esophago-gastro-duodenoscopy and an abdominal ultrasound scan: the results were normal.

Fasting plasma glucose, cortisol, LH, FSH, ADH, growth hormone, prolactin, TSH, FT3 and FT4 levels were measured and, since they were within the normal range, a dysfunction of the hypothalamic-pituitary axis was excluded. However, because of the presence of polyuria, even if the plasmatic osmolality was low, the patient underwent magnetic resonance imaging of the brain, which showed the presence of partially empty sella (Figure 1). Ophthalmologic examination was negative.

Other biochemical measurements included plasma renin activity and aldosterone concentration, and were markedly elevated (1 847 pg/mL and 1 530 pg/mL respectively).

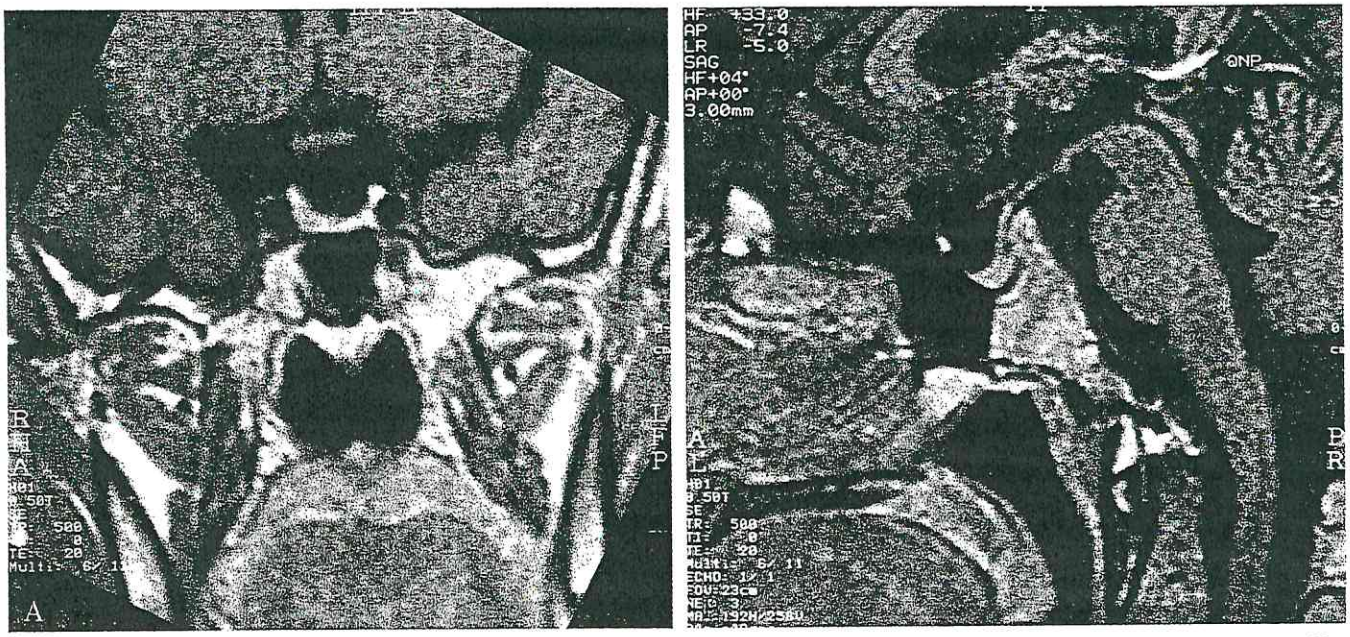

Figure 1.—Magnetic resonance (MR) scans in the coronal (A) and sagittal (B) planes, sighted in the sella turcica after gadolinium-enhancement. The MR images show a falciform hypophysis with 3 mm thickness from a 3D acquisition of the whole brain, laying down on the sellar floor with homogeneous contrast-enhancement (CE). Because of the pituitary volume reduction, herniation of the suprasellar cistern in the sellar cavity configures a classical empty sella image. Pituitary peduncle, optic chiasma and third ventricle are normal.

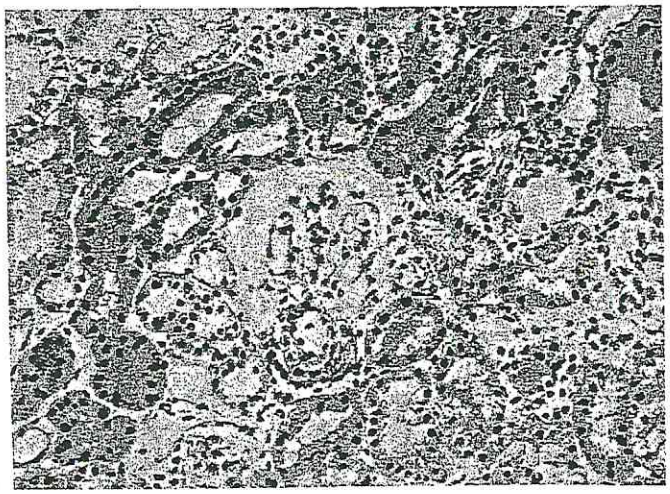

Figure 2.—Hyperplasia and hypertrophy of the juxtaglomerular apparatus (arrow) Hematoxylin-eosin ×400.

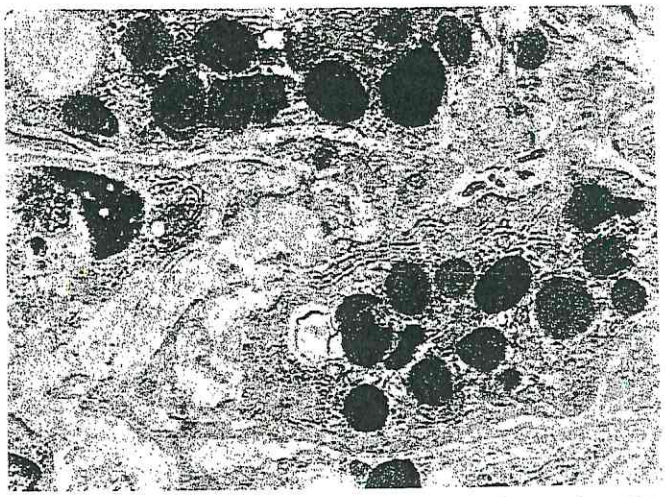

Figure 3.—Portion of the cytoplasm of a juxtaglomerular granular cell at electron microscopy with mature granules in black (magnification ×21.320).

A definite mechanism explaining all the symptoms was hypothesised and the causes of metabolic alkalosis with hypokalemia, normotension and hyperreninemic hyperaldosteronism run for the differential diagnosis.

On the grounds of clinical appearance and biochemical data, Bartter's syndrome was suspected. A renal biopsy was, therefore, performed, showing the presence of hyperplasia and hypertrophia of the juxtaglomerular apparatus (Figure 2): the diagnosis of Bartter's syndrome was confirmed by electron microscopy (Figure 3).

Good therapeutic effects were achieved using spironolactone (25 mg/day), ACE-inhibitor (5 mg/day) and potassium

TABLE I.—. *Features differentiating Gitelman syndrome, antenatal Bartter' syndrome, classical Bartter' syndrome, and our patient (modified from Bettinelli et al.[16]).*

	Gitelman syndrome	Bartter' syndrome type I-II	Bartter' syndrome type III	Our patient
Age at presentation	From childhood on	Prenatal, neonatal period	From the neonatal period on	28th year
Clinical signs/symptoms	Mild form Muscle weakness, abdominal pain, neuromuscular irritability	Severe form	Muscle weakness, growth retardation	Muscle weakness, headache, abdominal pain, nausea, vomiting
Polyhydramnios	—	++	—	—
Prematurity	—	++	—	—
Failure to thrive	+	+++	—/+	unknown
Polyuria/polydipsia	+	+++	+++	++
Tetany	++	—	—	+
Chondro-calcinosis	+	—	—	—
Nephrocalcinosis	—	++/+++	—	—
Laboratory examination				
Calciuria	Low	High	Normal-high	Low-normal
Magnesemia	Low	Normal	Normal	Normal

supplementation, with normalization of kalemia. The patient was discharged home some days later on the same therapy; at present, after 9 months of follow up, the symptoms have not recurred and the biochemical data are still in the normal range.

Discussion and conclusions

Bartter's syndrome, originally described by Bartter *et al.* in 1962,[12] is a group of closely related hereditary tubulopathies. All variants of the syndrome share several clinical characteristics including renal salt wasting, hypokalemic metabolic alkalosis, hyperreninemic hyperaldosteronism with normal blood pressure and hyperplasia of the juxtaglomerular apparatus.[13-15] Bartter's syndrome has been classified into 3 distinct phenotypes, each being characterized by different laboratory findings (Table I).[16]

Firstly, antenatal Bartter's syndrome, also known as hyperprostaglandin E syndrome,[17] is the most severe form of the disease. It is characterized by polyhydramnios, premature birth, life threatening episodes of salt and water loss in the neonatal period, hypokalemic alkalosis and failure to thrive, as well as hypercalciuria and early onset nephrocalcinosis.[13, 14]

Secondly, classical Bartter's syndrome occurs in infancy or early childhood. It is characterized by marked salt wasting and hypokalemia leading to polyuria, polydipsia, volume contraction, muscle weakness and growth retardation. Hypercalciuria and nephrocalcinosis may occur.[14, 15]

Finally, Gitelman's syndrome is characterized by a milder clinical presentation in older children or adults.[18] Patients may be asymptomatic and present with transient muscle weakness, abdominal pain, symptoms of neuromuscular irritability, or unexplained hypokalemia. Hypocalciuria and hypomagnesemia are typical.[15]

This classification, related partly to the demonstration of mutations in the genes encoding for tubular chloride or potassium channels and partly to the clinical presentation, does not fit all cases, and the possible presence of overlapping syndromes has recently been supposed.[16]

From a laboratory point of view, our patient showed some typical features of both classical Bartter's syndrome (*i.e.* normal magnesemia) and of Gitelman's syndrome (*i.e.* hypocalciuria) (Table I).

We excluded that our patient was affected by hypokalemia due to pharmacological chronic depletion (diuretic and laxative); no evidence of chronic vomiting and diarrhoea was present; moreover, serum and urine magnesium values were normal.[9]

Our patient presented a low urine chloride level. Drug history, clinical and laboratoristic findings permitted us to exclude other causes that may produce such a metabolic derangement similar to that found in Bartter's syndrome. The list of such conditions includes: cystic fibrosis, surreptitious diuretic use, chronic administration of a chloride-deficient diet, bulimia, chronic vomiting, chloridorrhea, and abuse of laxatives.[14] In all of these conditions, except diuretic

use, the chloride content of urine will be low, and this is contrary to all forms of Bartter's syndrome.[19]

In our opinion this patient is neither a classical Bartter's nor a Gitelman's syndrome, but an overlap syndrome, confirming that phenotype of Bartter's syndrome is not so clear-cut and that phenotypic overlap may occur.

Finally, at magnetic resonance imaging, our patient was incidentally discovered to have a partial empty sella. The term "empty sella" indicates the presence of the herniation of the arachnoid into the pituitary fossa, with the compression of the pituitary gland. Patients usually exhibit normal pituitary function, implying that the surrounding rim of pituitary tissue is fully functional. Hypopituitarism, however, may develop insidiously, especially when the gland is more stressed.[20]

The present experience represents, to the best of our knowledge, the second case of an adult patient affected by Bartter's syndrome with partial empty sella and normal hypophyseal, thyroidal, adrenal and gonadal function: only Colussi *et al.*[8] reported in 1992 the case of a 52-year-old female who presented an empty sella and normal endocrinological data, associated with hypokalemia, hypomagnesemia, hyperreninism and hyperaldosteronism: in addition, she presented urinary electrolytes in the normal range.[8] So far, a few pediatric cases of Bartter's syndrome have been described in association with empty sella: in one case the diagnosis of antenatal Bartter's syndrome was made in a 12-month-old male patient and in the same period an empty sella was found.[6] The other 2 cases were reported by Bettinelli *et al.*:[7] they described 2 unrelated children affected by Gitelman's syndrome with empty sella in association with a GH deficiency. These papers discuss whether the growth retardation is due to the deficiency of GH related to the empty sella or if it is due to Gitelman's syndrome.

At present the value of this association remains unclear. Empty sella is a quite common find in unselected autopsies;[21] thus the association of empty sella and Bartter's syndrome may be an incidental result.

On the other hand, empty sella may be asymptomatic and this association could represent a possible trigger factor of the phenotypic overlap of the different Bartter's syndrome variants. In this regard, it should be emphasized that in our patient the symptoms occurred for the first time in adult age during the summer of 2003 that was characterized by unusually hot temperatures in Italy. It could be conceivable that the clinical expression of the disease in our patient with partial empty sella may have occurred when pituitary functions were fully stressed.

In conclusion, as well as supporting the lack of a clear-cut distinction of the clinical characteristics of Bartter's syndrome variants, the present case suggests the appropriateness of performing magnetic resonance imaging in these patients in order to evaluate and to better understand the association between Bartter's syndrome and empty sella.

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