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Neuroblastoma Presenting with Acute Kidney Injury, Hyponatremic-Hypertensive-Like Syndrome and Nephrotic Proteinuria in a 10-Month-Old Child

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Key Words

Neuroblastoma · Proteinuria · Acute kidney injury · Hyponatremic-hypertensive syndrome

Abstract

Neuroblastoma is the most common extracranial solid tumor in childhood. Its presenting signs and symptoms may be highly variable, depending on the location of the primary tumor and its local or metastatic diffusion and, rarely, with paraneoplastic syndrome such as opsoclonus-myoclonus-ataxia syndrome and gastrointestinal disturbances, due to autoantibodies or to aberrant secretion of vasoactive intestinal peptide. Herein we describe a 10-month-old child with neuroblastoma presenting with a complex clinical picture characterized by acute kidney injury manifested by renal insufficiency and signs and symptoms of tubulointerstitial damage, with polyuria, polydipsia, glucosuria, aminoaciduria and hypochloremic metabolic alkalosis, and of glomerular damage with heavy proteinuria. Imaging study documented a suprarenal mass enveloping the aorta and its abdominal and renal ramifications and bilaterally renal veins. This clinical picture shows some analogies with the hyponatremic-hypertensive syndrome concerning the renovascular disease; however, in absence of systemic arterial hypertension, the heavy proteinuria and the polyuria could be explained by sectional increased intraglomerular pressure, due to local renal blood vessels constriction. Hypochloremic metabolic alkalosis probably developed because of local production of renin, responsible of renin-

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angiotensin-aldosterone system activation, but above all because of chloride loss through sweating. The long lasting dehydration, due to vomiting, sweating and polyuria, caused prolonged prerenal failure evolving in proximal tubular damage manifestations.

Introduction

Neuroblastoma is the most common extracranial solid tumor in childhood and accounts for 7% of malignancies in patients younger than 15 years [1]. It originates from the sympathetic nervous system, and in particular from a developing and incompletely committed precursor cell derived from neural-crest tissues [2]. Neuroblastoma occurs sporadically in 98% of cases; a genetic defect is involved in the rare familial neuroblastoma. In the subset of cases of neuroblastoma presenting in the context of other congenital abnormalities of the neural crest, the association with a germline loss-of-function mutation of homeobox gene *PHOX2B* has been demonstrated; on the other hand, familial neuroblastoma not associated with other congenital disorders of the neural crest arises from activating mutations of the anaplastic lymphoma kinase (*ALK*) oncogene, whose somatic mutations are, however, observed in sporadic cases of the disease [2]. Due to the widespread presence of the sympathetic nervous tissue in various body organs and apparatus, the presenting features of neuroblastoma may be variable, depending not only on the location of the primary tumor but also on the frequent metastases [1]. Systemic symptoms due to aberrant catecholamine excretion may be observed. Furthermore, in young children, neuroblastoma exceptionally manifests with paraneoplastic opsoclonus-myoclonus-ataxia (POMA) due to antineuronal nuclear (anti-Hu) antibodies [3] which have also been associated with gastrointestinal disturbances, such as constipation, gut dysmotility and paralytic ileus [4]. On the contrary, watery diarrhea due to aberrant vasoactive intestinal peptide secretion may be the presenting symptom in some cases of differentiated neuroblastoma [5].

Proteinuria is not part of the presenting features of childhood cancer. In patients with neuroblastoma it has been reported only in a 4-year-old boy with abdominal neuroblastoma [6]. We report a case where proteinuria was the initial reason for medical evaluation in a child with neuroblastoma.

Case Report

A 10-month-old girl was admitted to our hospital for investigations for nephrotic-range proteinuria. She was born to unrelated, Italian, healthy parents, by spontaneous delivery at the 38th week of an uncomplicated pregnancy; her birth weight was 3,110 g. Her growth and development were normal until the age of nine months, when she began vomiting, feeding poorly, sweating copiously, and losing weight. On admission, physical examination showed poor clinical conditions, with hypotonia and moderate dehydration. Her weight was 7,220 g (<3th percentile), reduced from having previously reached 8,450 g; her length was 68 cm; her body temperature was 37.5°C with a heart rate of 150 beats/min and respiratory rate of 46 breaths/min; blood pressure was normal on repeated measurements (82/43 mm Hg). Complete blood cell count showed leukocytes 12,800/mm³, red cell count 7,160,000/mm³, hemoglobin 15.7 g/dl, platelets 501,000/mm³. Blood urea nitrogen was 28 mg/dl (10.23 mmol/l), creatinine 1.5 mg/dl (132.60 μmol/l), glucose 92 mg/dl (5.1 mmol/l), AST 25 IU/l, ALT 42 IU/l; total plasma protein level was 7.9 g/dl, with albumin 56.9% (4.2 g/dl), α1 7.3%, α2 21.3%, β1 6.3%, β2 3.4%, γ 4.8%; uric acid was 8.5 mg/dl, sodium 138 mmol/l, potassium 3.2 mmol/l, chloride 88 mmol/l, venous pH 7.55 with a partial pressure of carbon dioxide of 29.2 mm Hg (probably due to

crying and hyperventilation), bicarbonate 27.8 mmol/l and BE +4. The AT III activity was 100%, prothrombin activity 100% and aPTT 29 s, serum lactate dehydrogenase was 376 IU/l and ferritin 5.9 μ mol/l (normal value for age 7–140 μ mol/l). She had polyuria and hypostenuria (diuresis 125 ml/kg/24 h); urinalysis revealed nephrotic-range proteinuria (6,100 mg/24 h) with albuminuria 4,540 mg/24 h, urinary loss of IgG 107 mg/24 h, and A1 microglobulin 29.4 mg/24 h; mild glucosuria (39 mg/dl) and aminoaciduria were also found, without hematuria or casts; urinary pH was 7.5 and urinary density 1,005. Urine culture was found sterile. Electrocardiogram revealed sinus tachycardia 180 beats/min; echocardiogram showed very mild concentric left ventricular hypertrophy, however, without pathological features. An endocrinologic evaluation revealed increased plasma renin (8 μ g/l/h; reference range 1.0–4.5 μ g/l/h) and aldosterone (4.83 nmol/l; reference range 0.1–0.8 nmol/l) levels, while cortisol and thyroid hormones were within the normal range; plasma erythropoietin was 42.6 mU/ml (reference range 3.7–37.5 mU/ml). Urinary excretion of vanillylmandelic acid was increased to 11 mg/24 h (1.57 mg/kg/24 h; reference range 0.1–0.18 mg/kg/24 h), while catecholamines were in the normal range, except for the normetanephrine and noradrenaline, which were also elevated (normetanephrine 1,537 μ g/24 h, reference range 88–440 μ g/24 h; noradrenaline 120 μ g/24 h, reference range 0–10 μ g/24 h).

The ultrasound abdomen examination revealed a solid, suprarenal mass on the left side, sized 2 × 2 cm; the right kidney showed slightly increased echogenicity on the upper side. Doppler ultrasonography showed no abnormal findings. High-resolution CT showed an abdominal mass sized 5 × 5.8 × 10.7 cm, localized between the vertebral bodies D9 and L3 and the aorta, enveloping the celiac tripod, the superior mesenteric artery and bilaterally the renal vessels. The upper half of the right kidney showed an area of reduced perfusion, while the left kidney showed abnormal tissue density. Adrenal glands were not identifiable in the context of the tumor mass, in which some calcifications were recognizable. Histopathology showed a tumor with a low grade of neuroblastic differentiation, with mitosis-karyorrhexis index (<2%) and elevated mitotic activity.

Discussion

In this patient, the presenting signs and symptoms of neuroblastoma included severe dehydration, polyglobulia, tubulointerstitial damage with acute kidney injury and renal insufficiency, electrolyte and acid-base unbalancing and heavy glomerular proteinuria. Although diarrhea and dehydration may be observed at presentation of neuroblastoma, tubular alterations are definitely unusual. We have been able to identify only one case previously: a 4-year-old boy affected by neuroblastoma presenting with nephrotic syndrome has been described in 1979 and renal histology demonstrated membranous glomerulonephritis due to immune complex [6].

On the other hand, POMA syndrome and gastrointestinal disturbances are associated with anti-Hu antibodies [3], and furthermore, the development of immune complex has been demonstrated in mice with C1300 neuroblastoma tumors confirming the tendency of neuroblastoma to produce immunologic paraneoplastic diseases [7]. Nevertheless, in a recent study performed on a broad series of adults with solid tumors, the prevalence of rheumatic syndromes was only 2.65%, and none of them manifested nephropathy, which shows the exceptionality of those manifestations also in adult patients [8].

In our opinion, the physiopathology of the complex clinical picture of the case we describe herein is not ascribable to autoimmune pathogenesis, but rather to a hemodynamic mechanism, subsequently complicated by a series of other physiopathologic phenomena. The sequence by which the events presumably developed is illustrated in [figure 1](#). The initial event was the development of the tumor mass from the adrenal glands and its extension upwards to envelope the great abdominal blood vessels and bilaterally the renal vessels. The meaningful feature is that the disruption of renal blood supply and the hemodynamic consequences have been different in the various areas

of renal tissue, as revealed by sonography and CT findings. So, local increased intraglomerular pressure could prime the development of the hyponatremic-hypertensive syndrome, characterized by glomerular hyperfiltration with proteinuria, polyuria, acid-base and electrolyte unbalancing, as rarely described in children with renovascular systemic hypertension [9–11]. Although in those circumstances, as expected, the consequence of the proteinuria is the development of nephrotic syndrome, in other cases the plasma albumin inexplicably remains at a normal level, even in case of lasting and massive albuminuria, as in our patient [11–14]. We could speculate that the severe dehydration, following copious sweating, vomiting and polyuria, caused such hypovolemia with hemoconcentration that plasma albumin concentration persisted beyond the threshold of edema. Also the polyglobulia could be explained by the same mechanism, even if another factor could have been the increased production of erythropoietin, probably stimulated by local renal parenchyma hypoxia. Hypovolemia was also responsible for the mild activation of the renin-angiotensin-aldosterone system and perhaps for metabolic alkalosis with hypochloremia and hypokalemia, but the loss of chloride through sweating was likely the most important cause of this phenomenon. Hypovolemia and the disruption of local renal blood circulation caused acute kidney injury and the signs and symptoms of proximal tubular damage, as glucosuria and aminoaciduria. On the other hand, the profound hypochloremia was the cause of the metabolic alkalosis, instead of metabolic acidosis typically associated with proximal tubular damage. Increased vasoactive amine secretion from neuroblastoma is not infrequent, and may cause elevated, although usually not severe, hypertension.

In conclusion, in our 10-month-old child, alteration of the renal function, at both the glomerular and tubular levels, were the presenting features of neuroblastoma, resulting from multiple pathogenic mechanisms. Our report furthermore emphasizes the high variability and various facets of the clinical manifestations of neuroblastoma.

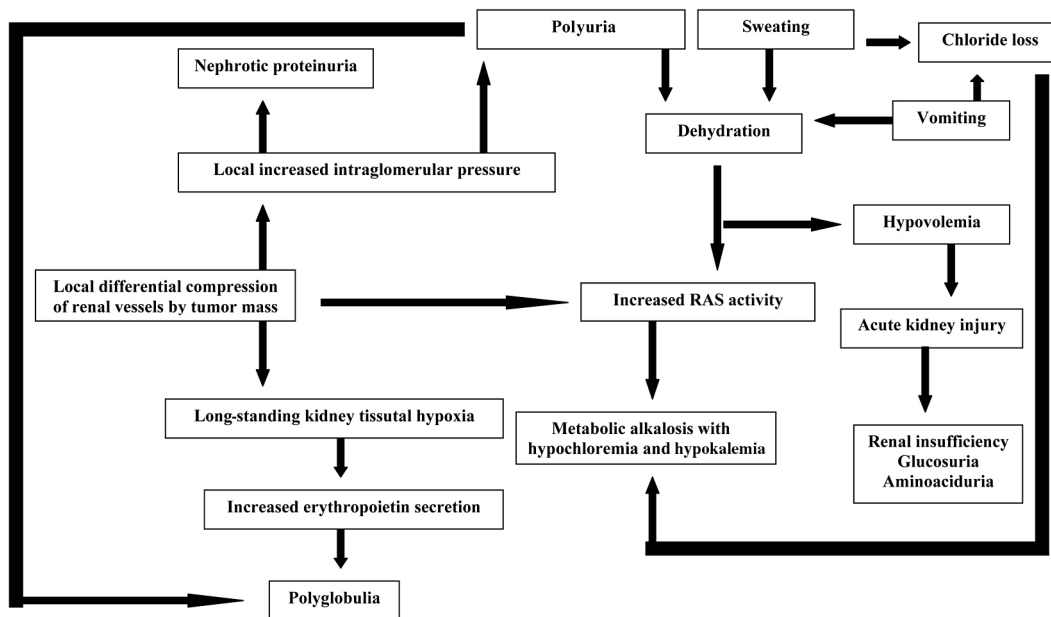


Fig. 1. Sequence of the events causing the complex clinical picture.

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