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Case Report

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A Rare Form of Neurocristopathy: Congenital Central Hypoventilation Syndrome, Ganglioneuroblastoma and Hirschsprung´S Disease

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List of Abbreviations

CCHS: Congenital Central Hypoventilation Syndrome
HD: Hirschsprung Disease
CT: Computed Tomography
GN: Ganglioneuroblastoma
MRI: Magnetic Resonance Imaging

Introduction

The term neurocristopathy was first suggested in 1974 by Bolande l, for a group of diseases secondary to a disturbance of growth, migration or cyto differentiation of cells derived from the neural crest. He considered two basic forms of presentation: the simple (ex. Hirschsprung disease; neuroblastoma; ganglioneuroblastoma; pheochromocytoma) and the complex or syndromic (ex. von Recklinghausen disease; multiple endocrine adenomatosis and associations of the simple forms).

In 1978 Haddat et al described, for the first time, the association between the Congenital Central Hypoventilation Syndrome (CCHS) and Hirschsprung disease (HD), confirmed through later similar descriptions In 1994 El-Halaby and Coran presented 3 cases of Hypoventilation and Hirschsprung disease and reviewed the literature for this association, finding a total of 26 cases. Three of those patients had coexisting malignant tumors (neuroblastoma 2 - ganglioneuroblastoma).

Congenital Central Hypoventilation Syndrome is a rare disorder, secondary to partial failure of the automatic control of breathing, characterized by alveolar hypoventilation, mainly during sleep. In 1992 Weese-Mayer et al (Gl, in the first systematic study of the CCHS, presented a series of 32 patients, five of them having also Hirschsprung's disease and one ganglioneuroblastoma (GN).

Until now only seven cases have been described associating Central Hypoventilation and Neuroblastoma/Ganglioneuroblastoma, five of them having also Hirschsprung disease.

In none of the published cases was there total recovery of the respiratory autonomy or was mentioned a late diagnosis of Hirschsprung disease. Also in none of the cases there was mention of an association with a congenital deficiency of coagulation factor VII [1, 2].

Case Report

J.B.A. 26 months old, Caucasian, male child, first born from healthy, non consanguineous parents. Family history was unremarkable. The pregnancy was routine and the mother traef. appropriate prenatal care..Cesarean section was done due to non-progression of labor and fetal bradycardia. The Apgar scores were 6, 7 and 8. Birth Weight was 2.770 grams.

The baby was hospitalized for 15 days, due to recurrent episodes of hypoventilation/ bradipnea, which resolved spontaneously without the need of mechanical ventilation.

After discharge, he was noticed to have some degree of food intolerance with abdominal distension, constipation with no stools for one or two days and growth failure, for which several different formulas were used, but with no significant improvement.

At two months of age, after the first dose of immunization (.Diphtheria+Tetanus+Pertussis, Poliomyelitis, Haemophilus influenzae type b) he had episodes of hypotonia and cyanosis, which was presumed to be seizures.

He was admitted to the PICU, showing hypoventilation, with respiratory acidosis, easily corrected with mechanical ventilation. He had a full and rapid neurological recovery and no evidence of pulmonary disease, but he continued to require mechanical ventilation, particularly during sleep due to severe hypercapnia, without signs of respiratory distress (tachypnea, dyspnea). After two months of ventilation there was progressive recovery of respiratory autonomy, initially when awake and later during sleep.

Abdominal and renal ultrasound including screening for detecting gastroesophageal reflux, EEG, metabolic screening, virologic studies, cardiac and ophthalmologic evaluations were all normal. A computed tomography (CT) scan and a magnetic resonance imaging (MRI) of the brain were also normal.

The polygraphic monitoring during sleep was compatible with the diagnosis of central hypoventilation. The only anomalies detected corresponded to three lumbar punctures (days 1, 7 and 11), the first one with increased cells and proteins. (cells 115 - protein 72) and the following two with albumin-cytological dissociation (cells 1.8 protein 72). In view of all the above, a diagnosis of central hypoventilation following meningoencephalitis was made, and the patient was discharged home aged 4.5 months, under domiciliary monitorization of apnoeas.

Due to persistent prolonged partial thromboplastin time, during admission, he was also diagnosed to have a congenital deficiency of coagulation factor VII (9.5%), both his parents having also a partial deficiency in this coagulation factor.

After discharge he maintained discrete constipation, requiring volume laxatives, high fiber diet and anal stimulation with micro enemas, all these allowing the child to pass stool daily or every other day.

At 12 months of age psychomotor development (PMD) was equivalent to 9 months, with moderate hypotonia and he had only moderate weight gain, thus reaching the 5th percentile. At that time he also had an EEG and an ophthalmologic evaluation that were both normal.

At 20 months old, he had a PMD equivalent to 17 months and a weight between the >10 <25 percentiles. A motility disturbance of the left eye was noted and a head computed tomography (CT) scan revealed a left front-orbital tumor Through a neurosurgical approach an extensive tumor mass could be observed, adherent to the dura and to the orbit involving also the frontal bone.

The biopsy showed it to be a metastatic ganglioneuroblastoma. An abdominal CT scan demonstrated a voluminous, partially calcified, tumor of the right adrenal gland (7x7 cm). After bone marrow aspiration and biopsy, as well as isotopic studies with metaiodobenzylguanidine (MIBG), (which showed fixation in the right adrenal gland as well as in the frontal, iliac, femoral and tibial bones), the tumour was classified as stage IV according to the International Neuroblastoma Staging System (INSS).

He had four cycles of chemotherapy (Cisplatin; VP16) according to protocol NB 08-92 of the Société Française d'Oncologie Pédiatrique ·(SFOP), with significant reduction in tumor size (3x3x4 cm), an increased number and extension of the tumor calcifications and disappearance of fixation of MIBG in the lower limbs.

In accordance with the chosen protocol and because there were no alterations on chromosome 1p36, no N-Myc amplification and the tumor was aneuploid (all favorable prognostic factors), it was decided to remove the adrenal tumor. During surgery, in which total removal of the right adrenal tumor was performed, the surgeon found a largely dilated colon, suggestive of Hirschsprung disease, later confirmed by rectal manometry (absence of the anorectal reflex) and barium enema (transitional zone in the rectum a few centimeters above the anal canal) Considering the overall situation and prognosis, the short intestinal segment involved and the benign clinical evolution of the Hirschsprung disease it was decided to perform only an extended ano-recto-sphincterotomy (8cm). Histology and biochemistry (acetylcholinesterase and lactic dehydrogenase) confirmed the diagnosis Marrow autotransplantation was not performed because of persistent cranial lesions. A new course of chemotherapy and radiotherapy to the front-orbital lesion were proposed, but the child's parents refused both. After one year there are no clinical or laboratory findings of tumor disease progression [3, 4].

Discussion

Both Hirschsprung disease and ganglioneuroblastoma have a common pathogenesis in the neural crest, corresponding to the present case, according to Bolande to a complex form of neurocristopathy. However, some clinical aspects differ in relation to previous descriptions, namely the late appearance and benign course of the Central Hypoventilation, the late clinical signs of Hirschsprung disease and the aggressive course of the ganglioneuroblastoma.

Congenital Central Hypoventilation Syndrome is a rare disorder involving abnormal central control of ventilation, probably by failure of the central chemoreceptors located in the ventro-lateral area of the medulla. The etiopathogenesis is not yet completely understood but the chromaffin cells of the carotid bodies, which also originate in the neural crest, do not seem responsible for the situation.

The association between Congenital Central Hypoventilation Syndrome with Hirschsprung disease, although rather infrequent, should not be taken as just occasional and the possibility that they have a common pathogenesis in the neural crest must be considered. Unlike this case, in the vast majority of the published ones, the Congenital Central Hypoventilation appears in the first few days of life. Diez Garcia described the oldest patient, who initiated at the age of three years, with ganglioneuroblastoma but without Hirschsprung disease.

Both in adults and children, cases are known of acquired Central Hypoventilation, secondary to neurosurgery, hypoxic-ischemic encephalopathy or meningoencephalitis. In this patient, the late appearance of hypoventilation and the spinal fluid alterations suggest an acquired form, secondary to meningoencephalitis. The favorable evolution also suggests a transitory lesion; in view that in CCHS no clear-cut case has been described in which there was total recovery of the respiratory autonomy [5-8].

Further, the association of ganglioneuroblastoma with Hirschsprung disease suggests Congenital Central Hypoventilation Syndrome (of an unusual benign course) as the most likely diagnosis. There are not previous reports of liquor alterations in CCHS.

In most patients, the congenital colonic aganglionosis associated with CCHS is total, serious and early diagnosed (s.a)_ The

course in this case should remind us that there are more benign forms of Hirschsprung disease, that must be looked for in every child with constipation and namely in the context of central hypoventilation.

The tumoural component is the least frequent, only seven cases having been described in world's literature (ganglioneuroblastoma 4 neuroblastoma 3) We feel nevertheless, that it would be advisable to perform its systematic screening in all situations of Central Hypoventilation, even those of late or atypical development. In this patient, abdominal ultrasound examination were performed at 2.5 and 3 months, CT scan and cranial MRI at 3.5 months, EEG and ophthalmologic evaluations at 2 and 12 months, without the tumor or the very extensive metastatic dissemination having been found or even suspected. Should those patients perform routine abdominal ultrasound as well as serial determinations of Vanilmandelic acid (VMA), ferritin, enolase (NSE) and lactic dehydrogenase levels, in their first years of life? The increased risk of familial recurrence is known for certain forms ·of Neurocristopathy, as in von Recklinghausen and Hirschsprung disease, being also admitted for Central Congenital Hypoventilation.In the complex forms of Neurocristopathy the small number of cases described does not allow to characterize the genetic markers and the potential modes of inheritance, in spite of several studies in that area.

Inherited coagulation disorders are, except for hemophilia and von Willebrand disease, rather infrequent (15l_ Hereditary factor VII deficiency, an autosomal disorder, has been described in around 150 certified cases but it's presumed to be more frequent. Even if factor v less than 10% of normal,(as in this case) homozygotic patients are usually asymptomatic. In spite of that, during surgery recombinant factor Vl was administered (30 µgr./Kg initially every 3 hours, with progressive spacing), without any problems.

We have not been able to find references to the association of Neurocristopathy and Congenital Factor VII deficiency, so being unable, at this moment, to establish or exclude any etiologic, pathogenic or genetic relationship between the two entities [9-16].

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