ENDOCRINE POLYMORPHISM OF CHILDHOOD NEURIFIBROMATOSIS

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Abstract:

Introduction: Neurofibromatosis (NF) is an autosomal dominant disorder with a multisystemic involvement and a variety of problems presented in childhood. ***Objectives:*** The authors aimed to evaluate the endocrine pathology associated to patients diagnosed with NF. ***Material and method:*** Patients (0-18 years old) diagnosed with NF and admitted to the Endocrinology Departament of "Louis Turcanu" Children Emergency Hospital were studied over a period of 5 years from 2007 to 2012. The study protocol consisted in the family and patients' history, physical examination and anthropometric measurements. Serum levels of TSH, FT4 and FT3, GH, LH, FSH, testosterone or estradiol, DHEA, 17 OH progesterone, cortisol, adrenaline and prolactin were measured. The imagistic examination depended of cases and consisted in radiography, pelvic ultrasound or head MRI. ***Results and discussions:*** Our study lot comprised 12 patients (3 months to 18 years and 6 months) diagnosed with NF (type I - 91.6%) with a sex ration male: female 1:2. 33.4% children had a parents known with NF. Regarding of endocrine pathology associated, 58.4% of them had short stature secondary to GH deficiencies and one boy had gigantism caused by optic pathway gliomas responsible for GH hypersecretion. Half of the girls had abnormal menses due to the polycystic ovary syndrome. No cases of hypothyroidism or pheochromocytoma was encountered. ***Conclusions:*** Although NF pictures are characteristic, other rare conditions including endocrine pathology can be associated so clinical clues should be always sought and investigation should be performed for in these circumstances.

Introduction:

Neurofibromatosis (NF) is an autosomal dominant disorder, a heterogeneous multisystemic neurocutaneous disorders involving both neuroectodermal and mesenchymal derivatives, probably of neural crest origin, which can involve any organ system. The National Institutes of Health Consensus Development Conference has defined 2 distinct types: neurofibromatosis type 1 (NF1), or von Recklinghausen disease, which affects 85% of patients, and neurofibromatosis type 2 (NF2), or bilateral acoustic neuromas/vestibular schwannomas, which affects 10% of patients.

The manifestations of NF1 are the result of a mutation in or deletion of the NF1 gene responsible for the production of neurofibromin. Its role consists in tumor suppressor while its decreased production is associated with clinical manifestations. The NF2 gene product known as merlin serves as a tumor suppressor. Decreased function or production of this protein results in a predisposition to develop a variety of tumors of the central and peripheral nervous systems .

Multisystemic involvement is common, and a variety of problems may present in childhood. Some frequent pathology associated are optic and acoustic involvement, intracranial and spinal tumors, and an increased incidence of malignancies, endocrine disorders, autonomic involvement, GI tract involvement, hypertension, and vascular anomalies .

Objective:

The authors aimed to evaluate the endocrine pathology associated to patients diagnosed with NF .

Material and metod:

Patients (0-18 years old) diagnosed with NF and admitted to the Endocrinology Departament of "Louis Turcanu" Children Emergency Hospital were studied. Out study took place on a period of 5 years from 2007 to 2012. All these patients presented to our departments for other complaints and not those characteristic for NF. They were diagnosed with NF according to the following criteria :

1. Six or more café-au-lait macules, the greatest diameter of which is >5 mm in prepubertal patients, and >15 mm in post-pubertal patients
2. Freckling in the axillary or inguinal region
3. Two or more neurofibromas of any type or one plexiform neurofibroma
4. Two or more Lisch nodules in the iris
5. Optic glioma
6. A distinctive osseous lesion such as sphenoid dysplasia or pseudoarthritis
7. A first-degree relative with NF1 diagnosed according to the preceding criteria

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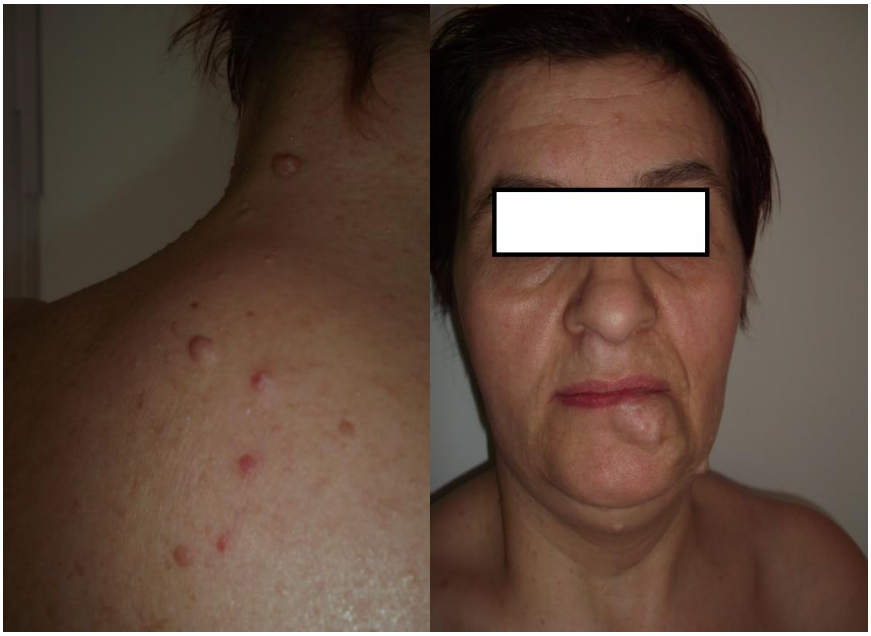

Figure 1 and 2: Clinical aspects of parents of RR child with NF

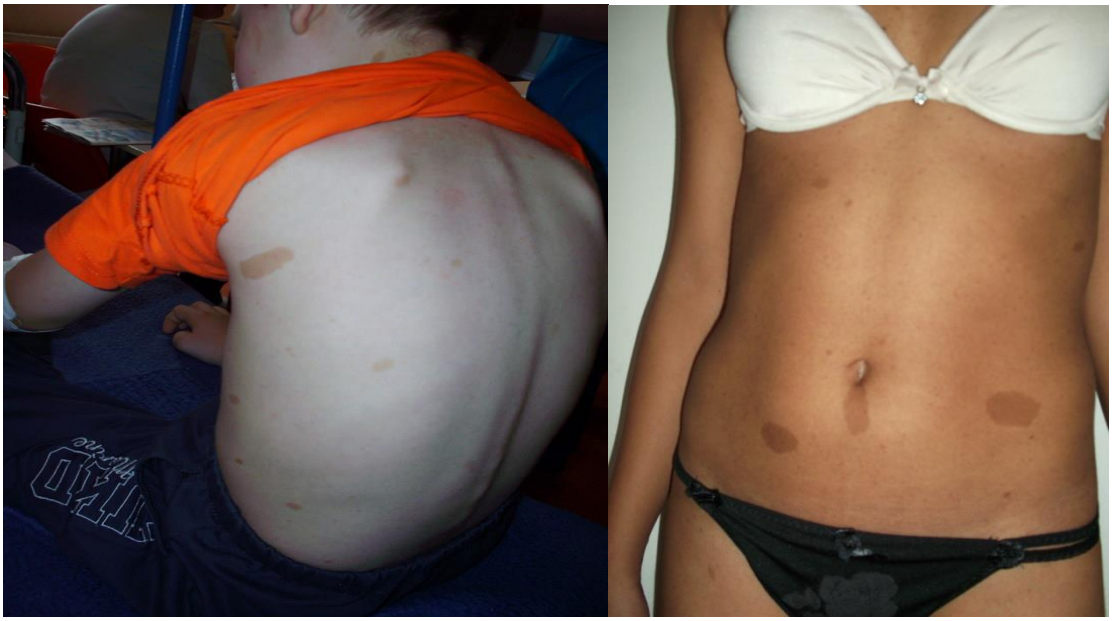

Figure 3 and 4: Clinical aspects - café-au-lait macules in IV boy 8 years old and RR 15 years old

Family's and patients' medical history were noted. They were clinical examined and anthropometric data (height, height standard deviation score, weight, body mass index, growth velocity) were measured clinically. Also it was noted the stage of pubertal development according to the Tanner criteria. Blood pressure was measured periodically and Holter examination performed in selected cases.

Serum levels of thyroid stimulating hormone, free T4 and T3, lutheinizing hormone, follicle stimulating hormone, testosterone or estradiol, DHEA, 17 OH progesterone , cortisol, adrenaline and prolactin were measured in all patients periodically. Catecholamine, metanephrine and vanillylmandelic acid levels in the 24-h urine collection were tested in order to diagnosed pheochromocytoma. The pituitary growth hormone reserve and the stimulating

growth hormone test and the serum level of IGF1 was assessed in patients with height deficiency.

Bone age determinations were performed at every year in selected cases. Other imagistic evaluation consisted in pelvic transabdominal ultrasounds and head MRI scan in cases with neurological symptoms.

Data were statistically analyzed using SPSS version 16.00. This study complied with the Declaration of Helsinki and has been approved by our institutional Ethics Committe somatostatinergic tone, increased GH release and loss of pulsatility . Specific tumor therapy is not indicated for this patient in the absence of mass effect or visual disturbance, but when these manifestations are presented, surgery, radiation, and/or chemotherapy should be done. Medical literature recommended the treating of GH excess with somatostatin analogue (Octreotide). Sometime, precocious puberty can developed as a side effect of this treatment . Unfortunately his parents refused any treatment and other medical advices because they belong to specific religious group.

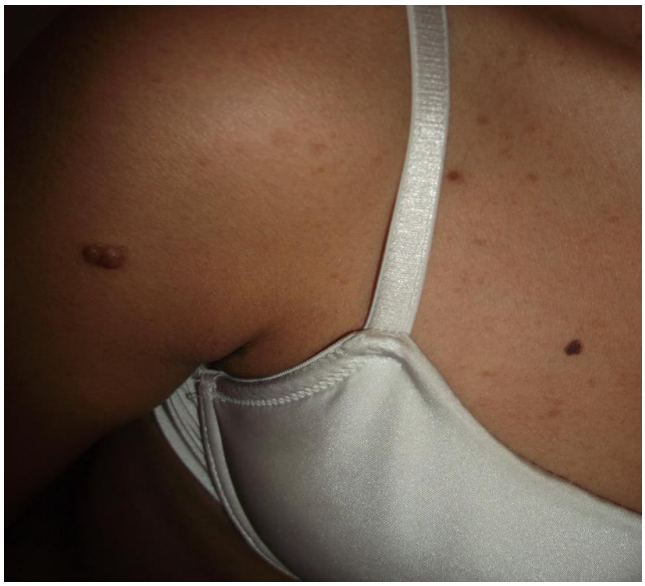

Figure 5: RR 15 years old clinical aspect – neurofibromas

Results and discussions:

Our study lot comprised 12 patients diagnosed with NF with a sex ration male: female 1:2. The patients' age ranged between 3 months to 18 years and 6 months. Only 4 children had their parents known with NF (Figure 1 and 2).

All the patients fulfilled the needed criteria, the majority of them being diagnosed as type I of NF (91.6%).

Regarding the anthropometric data, the majority of patients had short stature (58.4%) for their age as presenting in figure 6.

These patients with short stature (defined as a height that is equal to or more than 2 standard deviations below the population mean) had lower values of basal and stimulated GH (using clonidine or insulin-induced hypoglycemia as GH secretagogues) secondary to GH deficiency. (Figure 7). It is well known that short statute a feature of NF1, affecting approximately 13% to 24% of prepubertal patients and >40% of adults . In our study the prevalence of short stature was higher. Short stature associated with NF1 usually affects the skeleton symmetrically but scoliosis or deep plexiform neurofibromas, or the use of psychostimulant medications for the treatment of attention deficit disorder characteristic to the NF can interference with the normal skeletal development , . In our cases, 4 patients associated mild form of scoliosis with good evolution and without the need of surgical treatment.

One boy was diagnosed with gigantism secondary to the GH hypersecretion. Elevated serum level of prolactin was observed also. His MRI revealed the presence of optic pathway gliomas responsible for this hypersecretion. The mechanism consisted in the infiltration of the somatostatinergic pathways by the tumor leading to loss of

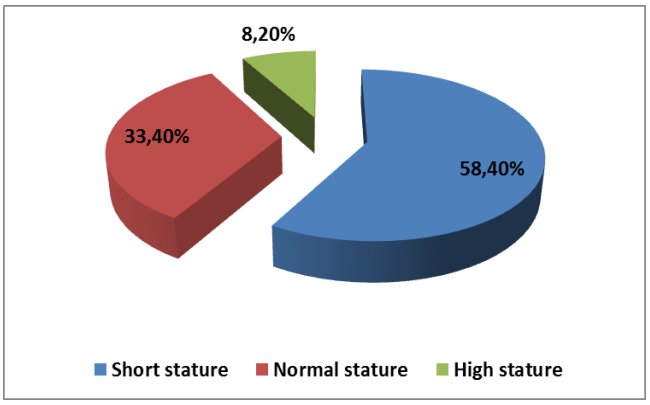

Figure 6: Distribution of patients studied according to their height

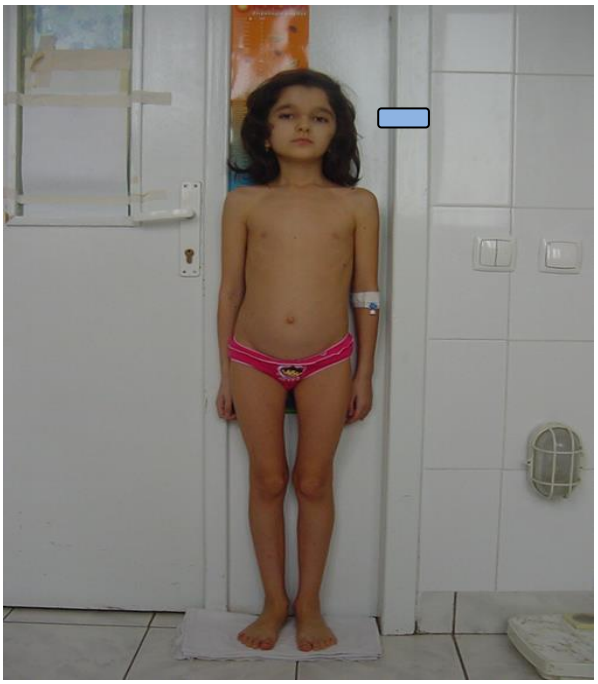

Figure 7: AD 19 years with NF and short stature

In children with NF, the most prevalent hormonal disorder is central precocious puberty, with a frequency of 3% compared to 0.06% in the general pediatric population . Half of the girls had polycystic ovary syndrome suggested by abnormal menses, increased values of DHEA, 17 OH progesterone and characteristic aspects at transabdominal pelvic ultrasound.

Pheochromocytoma is the most common endocrinopathy in adults with NF1, occurring in approximately 1% of adult patients and 0.1%-5.7% in children , but we have encountered no patients with such pathology in this study. Four children with NF had increased values of blood pressure at Holter examination, but their laboratory data were normal and no other suggestive clinical signs or symptoms were presented.

Conclusions:

NF is one of the most common phakomatoses encountered worldwide. Although its clinical pictures is characterized by the associations with intracerebral tumours, in specific scenario, other rare associations including endocrine pathology should be kept in mind, and clinical clues and investigations should be always sought for in these circumstances.

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