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DIVERSITY OF ENDOCRINE DISORDERS IN PATIENTS WITH NEUROFIBROMATOSIS IN CHILDHOOD: CASE REPORTS

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Abstract

Neurofibromatosis type 1 is a disorder characterized by an increased risk of formation of benign and malignant tumors due to the gene mutation on chromosome 17q11.2. During embryogenesis the gene product – neurofibromin regulates the proliferation and maturation of glial and neuronal progenitors. Loss of neurofibromin leads to activation of proto-oncogene, resulting in increased risk of tumor development. The incidence is described to be as 1:2,500 - 1:3,500 live births. It is an autosomal dominant disorder that affects the bone, nervous system, soft tissues, and skin. About 50% of children with Neurofibromatosis type 1 are affected by brain gliomas involving the visual pathways and/or the hypothalamic region. Brain Magnetic resonance imaging may reveal optic pathway gliomas, astrocytomas. About 50% of children with Neurofibromatosis type 1 are affected by brain gliomas involving the visual pathways and/or the hypothalamic region. Growth hormone deficiency is described as more common in children with Neurofibromatosis type 1, compared to the general population. Individuals with Neurofibromatosis type 1 are predisposed to brain tumors, and the vast majority of these tumors are pilocytic astrocytomas of the optic pathways and brainstem. Central precocious puberty development seems to be due to the near hypothalamic or suprasellar optic gliomas, leading to a premature activation of hypothalamic-pituitary-gonadal axis. The mechanism of growyh hormone deficiency is also connected with either tumor lesions or to insufficiency of growth hormone and IGF-1 due to loss of neurofibromin action in the pituitary cells. In the current work we describe two different endocrine disorders in children with Neurofibromatosis type 1, stressing the diversity of endocrine clinical presentation of the same main disease. The theory of central precocious puberty development in children with optic gliomas near to hypothalamic region is explained by interference with tonic central nervous system inhibition of the hypothalamic-pituitary-gonadal axis, resulting in the premature activation of the puberty. Described clinical cases present the heterogeneity and unpredictable progression of clinical features in children with Neurofibromatosis type 1. We underline the need of a careful diagnostic follow-up in all children with Neurofibromatosis type 1, particularly with an optic gliomas to recognize early symptoms of secondary endocrine disorders and early perform an appropriate treatment.

Keywords: *neurofibromatosis type 1, precocious puberty, optic gliomas.*

Introduction

Neurofibromatosis type 1, also known as von Recklinghausen neurofibromatosis, is an autosomal dominant multisystemic neuro-cutaneous disorder primarily affecting skin, bone and the nervous system [*Reynolds R et al., 2003; Boyd K et al., 2009; Hirbe A, Gutmann D, 2014*]. The responsible gene is on chromosome 17q11.2 [*Arun D, Gutmann D, 2004; De Luca A et al., 2005*]. During embryogenesis the gene product – neurofibromin regulates the proliferation and maturation of glial and neuronal progenitors. Loss of neurofibromin leads to activation of proto-oncogene, resulting in increased risk of tumor development [*Ferner R, Gutmann D, 2013*]. The incidence is described to be as 1:2,500-3,500 live births [*Bizzarri C, Bottaro G, 2015*].

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About 50% of children with neurofibromatosis type 1 are affected by brain gliomas involving the visual pathways and/or the hypothalamic region. Brain Magnetic resonance imaging (MRI) may reveal optic pathway gliomas and astrocytomas [*Hidehiro Takei, 2015; Evans D et al., 2017; Campen C, Gutmann D, 2018; Miller D et al., 2019*].

Central precocious puberty (CPP) in children with neurofibromatosis is linked to the early activation and maturation of hypothalamic-pituitary-gonadal axis, which is described in the literature to be present in 3% of neurofibromatosis type 1 cases. The theory of CPP development in children with optic gliomas near to hypothalamic region is explained by interference with tonic central nervous system inhibition of the hypothalamic-pituitary-gonadal axis, resulting in the premature activation of the puberty [*Kotwal N et al., 2012; Jiménez P et al., 2013; Campen C, Gutmann D, 2018*].

Short stature and macrocephaly are described as specific clinical features of children with Neurofibromatosis type 1 [*Karvonen M et al., 2013*]. Growth hormone (GH) deficiency is described as more common in children with Neurofibromatosis type 1, compared to the general population. It is also known that GH deficiency is more common in children with intracranial tumor and is correlated with the radiotherapy treatment of these tumors [*Howell S et al., 2000*]. We describe clinical cases of two children with Neurofibromatosis type 1 with different endocrine disorders presentation.

CASE REPORT 1

A 4.5 years old girl was referred by the neurologist to the pediatric endocrinologist with complaints of growth and bone age acceleration and enlargement of breasts. She was diagnosed with Neurofibromatosis type 1 at the age of 2.5 years old. The child had multiple irregularly shaped hyperpigmented spots - Café au lait macules. On MRI an optic glioma of a small size was found near the hypothalamic region, which showed no increase in size during last year on the second MRI. The stable size of optic gliomas served as a base not to remove it surgically. Bone age was accelerated from the chronological age and corresponded to 7-7.5 years. Height standard deviation score was +1.8SD. Mammary glands were palpable and were visualized by ultrasound examination. Baseline hormones measurement showed a normal thyroid and adrenal function, insulin-like growth factor (IGF1) and GH were in age adjusted normal ranges. Estradiol was 5.2*pg/ml* (NR<5), LH was 1.2IU/L, FSH was 4.2 *IU/L*. A stimulation test with gonadotropin-releasing hormone (GnRH) analogue was performed, which revealed LH release 13.5 *IU/L*, and FSH release of 21 *IU/L* after 1 hour after medication injection. This confirmed the diagnosis of central precocious puberty, requiring the treatment with GnRH analogues of long-action. The child's diagnosis was Neurofibromatosis type 1, hypothalamic optic gliomas, CPP. Now the child is 5.5 years old, height velocity and bone age acceleration is stopped, bone age corresponds to 7.5 years of age. Mammary glands showed no further enlargement on ultrasound examination.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

CASE REPORT 2

A 2 years old boy was admitted to the hospital because of severe loss of weight and weakness. The laboratory tests revealed hypernatremia. The physical examination revealed numerous café-au-lait spots of various size (larger than 5 *mm*), disseminated on all over the body (Figure) and freckling in the axillary and the inguinal area. The clinical examination of the parents revealed the presence of nine café-au-lait spots disseminated on the body skin of the child's father.

Anamnesis: his symptoms started from 1 year of age. Brain MRI revealed multiple lesions included pilocytic astrocytoma of third ventricle and optic gliomas. The child underwent the surgery for third ventricular tumor. On the day following surgery he presented polyuria with sodium 149 *mEq/L*, plasma osmolality 301 *mOsm/kg*, and urine osmolality 293 *mOsm/kg*. He started nasal desmopressin 0.05 *mg/day* with good response. He also started on dexamethasone 4 mg and levothyroxine 37.5 *mcg*, and then was referred to the pediatric endocrinologist. Levothyroxine dose was titrated, and dexamethasone was changed to hydrocortisone 30 *mg/day*. At the admission 150 *mg/hydrocortisone* infusion was initiated, after

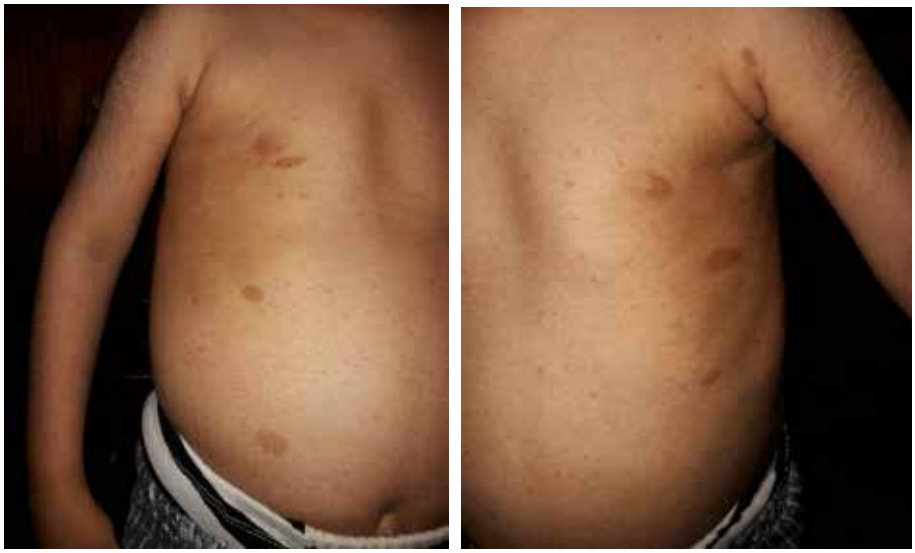

Figure. *Presentation of the skin lesion with multiple café-au-lait spots in a child with* neurofibromatosis *type 1.*

which sodium was stabilized and corresponded to 132 *mEq/L*. Now the child is 5 years old, height standard deviation score is -3.8*SD*, optic gliomas size is stable on the last 2-3 MRI, but due to the inoperable optic gliomas GH therapy is not initiated yet. The child's diagnosis is Neurofibromatosis type 1, secondary hypothyroidism, hypocorticism, diabetes insipidus and GH deficiency. He receives therapy with hydrocortison, levothyroxin and desmopresin.

Discussion

Neurofibromatosis type 1 can be associated with different endocrine disorders from short stature, GH deficiency to the CPP due to intracranial tumors [*Pinson S, Wolkenstein P, 2005; Strow R et al., 2016; Elwatidy S et al., 2017*]. Individuals with Neurofibromatosis type 1 are predisposed to brain tumors, and the vast majority of these tumors are pilocytic astrocytomas of the optic pathways and brainstem [*Hernández-Martín A, Duat-Rodríguez A, 2016; De Schepper S, 2005*]. CPP development seems to be due to the near hypothalamic or suprasellar optic gliomas, leading to a premature activation of hypothalamic-pituitary-gonadal axis. The mechanism of GH deficiency is also connected with either tumor lesions or to insufficiency of GH and IGF-1 due to loss of neurofibromin action in the pituitary cells. In the current work we describe two children with optic gliomas type 1, having different endocrine disorders associated with Neurofibromatosis. Described clinical cases present the heterogeneity and unpredictable progression of clinical features in children with Neurofibromatosis type 1. We underline the need of a careful diagnostic follow-up in all children with Neurofibromatosis type 1, particularly with an optic glioma to recognize early symptoms of secondary endocrine disorders and early perform an appropriate treatment.

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