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Case Report

Neurofibromatosis in Psychiatry: Late Diagnosis

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Abstract

Neurofibromatosis type 1 is a genetic disease whose manifestations may comprise psychiatric signs and symptoms, such as cognitive-behavioral deficit, dysthymia, anxiety and alcoholism. The disease usually manifests itself in childhood, but diagnosis is often late, which causes even more damage to the affected individual. Therefore, it is critical that health professionals and educators become familiar with the disease. This article presents a review of the pathology and reports a case whose diagnosis was made in adulthood, during hospitalization in a psychiatric ward.

Keywords: *Neurofibromatosis; Substance-Related Disorders; Intellectual Disability*

Introduction

Neurofibromatoses (NF) are a group of diseases of genetic etiology whose signs and symptoms in the affected individuals involve, particularly, the dermal, neurological, orthopedic and psychiatric systems, which highlights the importance of experts in their respective fields in addition to pediatricians and family health physicians being familiar with the clinical onset of the diseases, so as to diagnose NF at the earliest possible stage, which allows for a better clinical management, reduced morbidity of complications and better quality of life [1]. This text introduces a case report of a patient with NF1 whose diagnosis was too late, that is, in adulthood, based on clinical psychiatric signs that, together with the occurrence of skin lesions, suggested the diagnosis.

Epidemiology and etiology

NFs are genetic diseases that affect approximately 80,000 Brazilian citizens [1,2]. Its most common type is NF1, whose incidence ranges from 1/2,000 to 1/7,800 live births and is characterized by café-au-lait spots and cutaneous neurofibromas [2,3]. It is the most common autosomal dominant neurogenetic disease caused by mutations in the NF1 gene that is located in chromosome 17, responsible for encoding the neurofibromine protein [3,4]. Such protein is expressed in neurons and glial cells and is necessary for neural development [4]. Neurofibromina is also involved in cell proliferation and differentiation, and its loss may explain brain structure abnormalities, such as decrease in cortical and subcortical structure volumes, in addition to changes in white and grey matter [5].

Neurofibromatosis type 1 - Clinical criteria for diagnosis

In 1988, the National Institutes of Health Consensus Development Conference Statement: neurofibromatosis (NIH) established the criteria for diagnosis of NF1. Two or more of the following events are necessary for diagnosis: [3]

- Six or more café-au-lait spots larger than 5 mm in prepubertal children and larger than 15 mm in post-pubertal children.
- Two or more neurofibromas of any type whatsoever or a plexiform neurofibroma.

- Freckles (ephelides) in axillary or inguinal regions.
- Optic glioma
- Two or more Lisch nodules (iris hamartomas).
- A distinct bone lesion, such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis.
- A first-degree relative (parents, siblings or children) diagnosed with NF1 according to the above-mentioned criteria.

About 46% of patients up to 1 year of age do not fulfill the diagnosis criteria, however, almost all of them will fulfill such criteria until 8 years of age [6].

Psychic manifestations of NF1

The clinical polymorphism of NF1 is very broad. The same genetic mutation can cause severe symptoms in some individuals, while others present milder manifestations, which fact may be justified by genetic change associated with environmental factors [2,7].

Individuals with NF1 tend to present increase in volume of white matter in the frontal lobe and corpus callosum, as well as of grey matter in the nuclei of the thalamus and right caudate. Reduced white matter microstructure integrity suggests a decrease in effective structural connectivity. Studies have demonstrated deficits in the visual activation of occipital, temporal and parietal regions and abnormal involvement of the frontal lobe, in addition to neurochemical abnormalities. Gamma-aminobutyric acid levels (GABA) have decreased significantly in the occipital cortex. Such structural, functional and neurochemical changes to the central nervous system may cause learning disabilities [8].

The NF1 gene's function is that of regulating the release, in the central amygdala, of GABA, a neurotransmitter that reduces anxiety and increases the feeling of relaxation. Genetic variations in such gene may provide humans with an increased vulnerability and susceptibility to alcohol dependence [9].

Social disabilities, physical changes and poor levels of educational achievement explain why children and adolescents with NF1 a greater risk have of developing low self-esteem [10]. Additionally, behavioural changes and cognitive deficits are frequent phenomena in patients with NF1, and such intellectual disabilities comprise many neuropsicopathologies [5,11]. About 38% of the children with NF1 fulfill the criteria for diagnosis of attention deficit hyperactivity disorder (ADHD) [11].

Considering that, as years pass by, increased physical injuries take place, adults with NF1 tend to develop negative and stigmatized self-esteem, which makes the creation of interpersonal relationships difficult [12,13]. The need for medical follow-up, the uncertainty concerning disease progression, the social prejudice, the feeling of rejection as well as the difficulty finding jobs create very low self-esteem and precarious financial situations, thus causing a high level of psychological suffering [10,13,14].

A Swedish study followed for 12 years patients with NF1 and showed an increase in mortality rates, as well as an average reduction of 15 years in life expectancy. Psychiatric diagnoses were made in one-third of the patients, in that dysthymia is the most frequent (21%). Other reported disorders were generalized anxiety, dementia associated with alcoholism, mild mental retardation and organic personality disorder [15].

Case Report

J. E. M., 50 years of age, with incomplete primary school, single, retired for disability, was hospitalized in the psychiatric ward of Hospital Universitário São Francisco [São Francisco University Hospital] (HUSF) by the Centro de Atenção Psicossocial [Psychosocial Care Center] (CAPS) for alcohol addiction, bipolar affective disorder and had difficulty adhering to outpatient treatment.

In the initial interview, the patient reported having started consuming alcohol on a recreational basis at 20 years of age, with progressive increase in amount and frequency of such consumption. After having heavily consumed alcohol for 2 weeks, he had 4 convulsion seizu-

res. He used cocaine and crack for 10 years, and has been in abstinence of such substances for 9 years. He had been previously hospitalized five times, in that one of them was because of a psychotic break with visual and auditory hallucinations associated with the use of alcohol.

The patient reported depressive mood and has a background of 5 previous minor suicide attempts without clinical implications.

He denied having other comorbidities and said he attended the Psychosocial Care Center, however, without adhering to the treatment.

The family background includes a sister with mental retardation and another with depression. His father is alcohol-addicted.

The physical examination revealed presence of nodules in the abdomen and upper limbs. At that time, the hypothesis raised for such lesions was that of lipoma.

At the mental status examination, he was generally oriented, hypothymic with affection-like mood, without sense-perception alterations and with childish-like thinking.

The first diagnostic hypothesis was that of alcohol addiction and mood disorder, to be further clarified.

On the third day of hospitalization, during hospital visit for case discussion, the possibility of NF1 was considered when the physicians associated the patient's mental status with the skin alterations. Upon physical re-examination, multiple subcutaneous nodules were found in the patient's upper body, upper and lower limbs, in addition to café-au-lait spots in the upper body and axillary ephelides, thus fulfilling the diagnosis criteria for NIH. The diagnosis was confirmed through anatomopathological and immunohistochemical examinations of one of the subcutaneous nodules.

During the first week of hospitalization the patient was hypothymic, socially isolated and showed low threshold for frustration. By associating the polymorphic psychic symptomatology with the clinical and histopathological diagnosis of NF1, the suspicion of mental retardation was considered.

Raven's Progressive Matrix Test defined the patient's intelligence as lower than average, with signs of mental illness.

During hospitalization the patient was given anticonvulsant to prevent seizures and improve impulsivity control. Aimed at preventing alcohol abstinence syndrome the patient was given benzodiazepine for seven days, and a thiamine replacement was carried out. During the 22 days of hospitalization, the patient did not develop alcohol withdrawal symptoms or seizures. His mood was improved with the treatment, and he willfully engaged in occupational therapy. He cultivated ties with the team and his health developed positively in a short period of time.

Discussion

Notwithstanding the current knowledge on the etiology and clinical manifestations of NF1, such diagnostic hypothesis is not always considered by healthcare professionals. The reported case depicts such situation. The skin manifestations themselves should have been enough to consider NF1, which indicates lack of knowledge on the issue, or negligence in the performance of the physical examination and, together with the expressive and multifaceted psychiatric framework, it is crystal-clear that such diagnosis had not been considered for the individual in the outpatient care or during his previous hospitalizations. As a consequence, the patient and his family members have never been given any instruction whatsoever on his pathology, which fact made difficult not only the treatment and understanding of the disease and its comorbidities, but also prevented appropriate family and genetic counseling and psychosocial support from taking place for the individual's insertion into society. Awareness campaigns on the disease may be highly valuable in demystifying NF1, especially for educators, with the purpose of making early detection of the disease in school-aged children.

Conclusion

NF1 is a prevalent disease with polymorphic symptomatology and variable degrees of limitations, and may pass undetected in childhood and even in adulthood. Its prognosis is directly proportional to the earliness of its diagnosis, having impact on the health and quality of

life of its carrier and his/her family members. Thus, physicians, especially general practitioners, healthcare professionals and educators should be able to identify its early signs and point out a specialized multidisciplinary field.

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