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Neurofibromatosis Type 1 and Psychiatric Disorders: A Case Report and Literature Review

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Abstract **Case Report**

Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen disease, is a multisystemic neurocutaneous disorder with an autosomal dominant inheritance and variable expressivity. It affects all races with a sex ratio of 1 and a prevalence of 1 in 3,000 to 4,000 births, with 40 to 50% of cases being sporadic. Studies suggest that psychiatric disorders are more common in patients with NF1 than in the general population; the total prevalence of psychiatric pathology, across all diagnoses, is estimated at 33%. Two-thirds of these disorders are considered moderate to severe and vary from one patient to another. In this work, we will present the case of a 10-year-old child who was diagnosed with epilepsy at the age of 5 and with NF1 at the age of 6. The child was referred from the children's hospital to the child psychiatry department at Arrazi Hospital for management of behavioral problems, suicidal ideation, and academic difficulties. We will also review the literature on the psychiatric manifestations in patients with NF1.

Keywords: Neurofibromatosis type 1, psychiatric disorders, neurodeveloppmental disorders, Anxiety, neuropsychiatry, mood disorders.

1. INTRODUCTION

Neurofibromatoses (NF) are a group of genetic neurological disorders that frequently result in the formation of tumors on nerve sheaths and internal organs, affecting men and women equally. Each type of neurofibromatosis—Neurofibromatosis Type 1 (NF1), Neurofibromatosis Type 2 (NF2), and schwannomatosis—has distinct impacts on patients' lives.

Neurofibromatosis Type 1 (NF1) is an autosomal dominant genetic disorder caused by mutations in the NF1 gene, with a prevalence of 1 in 4,560. NF1 is characterized by café-au-lait spots, axillary or inguinal freckling, and optic gliomas, and is often considered a cancer-prone syndrome. The severity and clinical expression of NF1 vary widely, with some individuals experiencing mild, uncomplicated forms while others develop rare, complex manifestations affecting multiple systems within the body. This variability can even be observed within the same family. The NF1 gene, located on chromosome 17q11.2, encodes the tumor suppressor protein neurofibromin. When mutated, cellular growth regulation is disrupted, leading to the development of tumors known as neurofibromas. Although cutaneous neurofibromas are the most visible feature, NF1 can also affect vital internal organs, posing significant health risks and reducing life expectancy by approximately 10-15 years compared to the general population.

The unpredictable nature of tumor development and disease progression necessitates lifelong monitoring once NF1 is suspected. The numerous complications, including café-au-lait spots, cutaneous or plexiform neurofibromas, and malformations, present significant psychological challenges. The inability to predict disease progression and manifestations adds to the emotional burden. NF1 commonly affects the head and neck region, causing symptoms such as severe disfigurement, blindness, nerve compression, and airway obstruction.

Research indicates that up to 80% of children with NF1 may experience cognitive and behavioral issues. Over the past two decades, increasing research has identified several previously underappreciated neuropsychological aspects of NF1. However, the molecular mechanisms underlying these cognitive symptoms remain largely unknown. This paper aims to present the case of a patient with NF1 who exhibits a polymorphic psychiatric profile and review the existing literature on this subject.

2. CASE REPORT

This case report concerns a 10-year-old child enrolled in the fourth grade who was referred to our pediatric psychiatry service from the children's hospital for management of behavioral issues. During visits to his pediatrician, he is described as disruptive, interfering with the flow of the consultation due to his behavior. Additionally, during each visit, he steals items from the doctor's desk, most recently a prescription pad, which his mother noticed after leaving the hospital. Consequently, he was referred to our child and adolescent psychiatry service for intervention.

He is the younger of two boys from non-consanguineous parents. During pregnancy, his mother had treatment-resistant hypertension, requiring high-dose antihypertensive therapy. As a result, he was born prematurely at 28 weeks gestation via cesarean section, weighing 800 grams at birth. He remained hospitalized for two months before being discharged with a weight of 1500 grams. His psychomotor and language development were delayed; he began walking at age 2 and started speaking at 2 and a half years. Diurnal continence was achieved at age 7, but nocturnal continence remains unestablished. He still requires assistance with activities such as toileting and dressing. Academically, his performance has been poor; he repeated the first grade and struggles significantly with comprehension, reading, and writing, relying on educational modifications.

He has been under treatment for epilepsy since the age of 5, although seizures began earlier. He is managed with antiepileptic medications for pharmacoresistant epilepsy, having undergone several unsuccessful medication trials. He also has neurofibromatosis type 1, and stunted growth and development [at -2 standard deviations (SD)].

Regarding his behavior, his conduct has been inappropriate since the age of 5, initially manifesting as aggression and impulsivity. He has been reported to slap classmates without provocation, throw stones at passersby, and damage property, including car windows. His mother also reports a tendency towards fire, allegedly setting fire to toys, money, and papers, with repeated incidents of theft on a daily basis. His thefts are frequent and indiscriminate, taking items regardless of their utility (e.g., food from stores, medical prescriptions, his aunt's bracelet). He frequently engages in lying. Socially, he does not engage with peers, lacks the skills to interact with them, is unwelcome in group settings, and prefers the company of younger children, displaying significant immaturity relative to his age.

During the initial psychiatric examination, he presented as small in stature, calm in motor behavior, and superficially responsive with a slight smile, although he quickly became restless, fidgety, and touched items in the room, raising concerns about potential theft. His mood was neither sad nor euphoric, with no delusions or perceptual disturbances. His appetite remains normal, but he sleeps little, going to bed late and waking up early.

The diagnoses of conduct disorder, kleptomania, pyromania, intellectual developmental disorder, attention deficit/hyperactivity disorder (ADHD), and developmental coordination disorder were established following comprehensive assessments, including speech and motor evaluations, IQ testing, and Vineland scales.

3. DISCUSSION

Psychiatric manifestations associated with neurofibromatosis type 1 (NF1) are diverse and significantly more prevalent compared to the general population, with approximately 33% of NF1 patients experiencing moderate to severe psychiatric disorders. Numerous studies have explored the comorbidity of NF1 with various psychiatric conditions, including mood disorders, anxiety disorders, and neurodevelopmental disorders.

*** Dysthymia - Suicide Risk**

Psychiatric disorders are more common in patients with NF1 than in the general population; the overall prevalence of psychiatric pathology, across all diagnoses, is estimated to be 33%. Psychiatric disorders in NF1 vary from one patient to another. The most common disorders are mood disorders (dysthymia: 21%, depression: 7% of patients); anxiety disorders or neuroses (affecting between 1.5% and 6% of patients); personality disorders (3% of patients); and alcohol abuse or dependence (affecting between 3% and 8% of patients). The frequency of these disorders differs from that commonly observed in the general population. The suicide rate is reported to be higher than in the general population and other "medical" conditions. It is said to be four times higher in NF1 patients. This increased suicide risk needs confirmation from further studies, according to Harris and Barraclough. Zoller and Rembeck noted a significantly higher incidence of suicidal ideation in NF1 patients with psychiatric comorbidity. Similarly, Samuelson and Riccardi reported three cases of suicide attempts among 69 patients. In the same study, self-aggressive or hetero-aggressive behaviors were less frequent in patients compared to controls.

*** Anxiety Disorders**

Belzeaux and Lançon reported a prevalence of anxiety disorders in NF1 ranging from 1.5% to 6%. Studies have shown various psychiatric and behavioral disorders associated with NF1 in children, including anxiety, depression, obsessions and compulsions, and somatic complaints. Other research indicates that compared to their healthy siblings, children with NF1 experience significant internalizing problems, such as symptoms of anxiety or depression, withdrawal, and social difficulties. However, these psychiatric

morbidities are often underdiagnosed. Pasini *et al*., recently investigated anxiety manifestations associated with NF1. In their comparative study of 15 children and adolescents with NF1 using the Multidimensional Anxiety Scale for Children (MASC), they found that NF1 patients had higher scores than the control group. They concluded that these children are predisposed to develop anxiety disorders later in life. Wang *et al*., assessed anxiety using the "State-Trait Anxiety Inventory for Adults" in 133 adults with NF1. The anxiety levels reported by NF1 patients were higher compared to patients with other chronic diseases, such as coronary artery disease and cancer. However, this study did not find a relationship between the severity of skin involvement and emotional functioning.

***Neurodevelopmental Disorders**

Communication Disorders and Specific Learning disorder

Children with neurofibromatosis type 1 (NF1) frequently exhibit significant academic difficulties, with 52% showing problems with academic performance. Of these, 20% are diagnosed with specific learning disabilities, and 32% experience more general learning issues, with males potentially at higher risk for specific learning disabilities (Hyman *et al*., 2006). These children often demonstrate poor performance in reading, writing, spelling, organizational skills, and mathematics. Academic impairment is considered a major consequence of cognitive deficits in NF1, which can impact social outcomes in adulthood. Also, common phonological deficits, such as in phonological memory and grapheme-phoneme correspondences, increase the risk of reading and developmental disorders. Additionally, alterations in visual processing, particularly in the magnocellular and parvocellular pathways, and deficits in visual attention, are crucial factors in the reading difficulties and other neurodevelopmental challenges associated with NF1.

Attention Deficit Hyperactivity Disorder (ADHD)

It is reported that approximately 38% of children with NF1 have attention-deficit/hyperactivity disorder (ADHD). They often exhibit significant difficulties with selective and sustained attention, which can impact their learning and behavior, potentially leading to a diagnosis of ADHD, with or without hyperactivity. Unlike ADHD cases in the general population, children with NF1 rarely display hyperactive behaviors and are more likely to be diagnosed with the predominantly inattentive type or combined type of ADHD. A recent study comparing the intellectual and attentional profiles of NF1 children meeting ADHD criteria, NF1 children without ADHD, and children with primary ADHD revealed that NF1 children meeting ADHD criteria performed worst on attention tasks.

Autism Spectrum Disorder (ASD)

Recent studies indicate that approximately 25% of children with NF1 are diagnosed with ASD, a rate significantly higher than the 0.5–2.0% observed in the general population. Analysis of data from 531 NF1 individuals has shown a notable link between the severity of autistic traits and the specific location of mutations within the NF1 gene. Additionally, emerging research suggests that disruptions in Ras/MAPK signaling during development may contribute to the increased risk of ASD.

NB: The Ras/MAPK pathway regulates various important processes, including cell growth, differentiation, and survival. Mutations in the NF1 gene affect Ras regulation, leading to overactivation of the Ras/MAPK pathway, which contributes to tumor formation and possibly other neurological issues like ASD.

Motor Disorders

Motor disorders or developmental coordination disorder in young children often present as general clumsiness. As they grow, these challenges may evolve into difficulties with motor control, fine motor coordination, handwriting, spatial organization, or visuomotor integration. Additionally, these children frequently exhibit slowness in various areas, including motor skills, graphomotor tasks, task completion, and ideation. Significant fatigue is also commonly reported by both educators and family members, likely due to the increased attentional demands associated with their learning difficulties.

However, studies do not report cases of bipolar mood disorder, schizophrenia, or delusional disorder. There is one reported case of anorexia nervosa, one case of unspecified psychosis, and one case of neurocognitive disorders in older adults. Intellectual functioning is generally considered normal, but studies consistently highlight a shift towards the lower end of the IQ distribution in the NF1 population, with an average IQ around 90. Intellectual disability, defined as an IQ below 70, is rare, occurring in only 4% to 8% of individuals.

4. CONCLUSION

The comorbidity of psychiatric disorders with neurofibromatosis type 1 (NF1) has been documented in numerous studies. Current literature suggests that this association may be multifactorial. However, a critical question remains: are these psychiatric manifestations a result of a multisystemic disease? Further genetic and neurophysiological investigations are required to elucidate the psychopathological and etiopathogenic processes underlying this association.

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