WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Neurofibromatosis and Psychiatric Manifestations: Two Case Reports

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ABSTRACT:

Neurofibromatoses are part of a group of genetically inherited disorders transmitted in an autosomal dominant pattern, which impact the nervous system and predispose individuals to tumor formation. This group of heterogeneous genetic diseases includes Neurofibromatosis type 1 (NF1), the most common form—also known as peripheral neurofibromatosis or von Recklinghausen disease—and Neurofibromatosis type 2 (NF2), which is ten times rarer, along with other increasingly rare types that differ genetically and clinically. While the neurological component of these conditions is well documented, psychiatric manifestations remain underestimated and underexplored. This article aims to illustrate psychiatric comorbidity in two distinct forms of neurofibromatosis, through the presentation of two clinical cases. The first case involves a patient with NF1 presenting with a major depressive episode comorbid with mild intellectual developmental disorder, highlighting the psychological impact of the sensory and neurological complications associated with this form. The second case concerns a female patient with NF2 presenting with comorbid schizophrenia, underlining possible interactions between the neurodevelopmental alterations in NF2 and the emergence of psychotic disorders. Through these case reports, we discuss potential pathophysiological hypotheses, clinical implications, and the importance of a multidisciplinary approach that includes systematic psychiatric evaluation in patients with NF. Early recognition of these disorders could improve functional outcomes and patients' quality of life.

Introduction:

Neurofibromatoses are part of a group of genetically inherited disorders transmitted in an autosomal dominant pattern, which affect the nervous system and predispose individuals to tumor formation. This group of heterogeneous genetic diseases includes Neurofibromatosis type 1 (NF1), the most common form, also known as peripheral neurofibromatosis or von Recklinghausen disease; Neurofibromatosis type 2 (NF2), which is ten times rarer; as well as other increasingly rare types. The incidence of NF1 is approximately 1 in 3,500 births, and it is associated with a reduced life expectancy compared to the general population. It is caused by mutations in the polymorphic NF1 gene located on chromosome 17. The responsible protein is neurofibromin, which acts as a tumor suppressor [1]. Neurofibromatosis type 2, also referred to as central neurofibromatosis or formerly bilateral acoustic neuroma, is characterized by much less variable clinical manifestations. It generally appears during adolescence or early adulthood and includes the development of schwannomas—which alone are sufficient for diagnosis—as well as meningiomas and ependymomas. A juvenile cataract, observed in 40% of patients, is the only non-tumoral manifestation of NF2. The presence of bilateral schwannomas is one of its hallmark features. The gene responsible for this disorder is located on chromosome 22 [2]. Although traditionally approached from a neurological perspective, neurofibromatoses are increasingly recognized for their impact on patients' mental health. Several studies have highlighted a high prevalence of cognitive impairments and psychiatric comorbidities among affected individuals, including anxiety disorders, depressive disorders, attention disorders, and, more rarely, psychotic disorders. However, these manifestations are often underdiagnosed, despite their significant impact on quality of life and overall functioning. Through the presentation of these two clinical cases, this study aims to illustrate the diversity and severity of psychiatric manifestations in neurofibromatoses.

Case Reports:

Case 1:

Mr. B.A., a 36-year-old male, has been followed by the neurology department since the age of 9 for Neurofibromatosis type 1 (NF1), or von Recklinghausen disease. The diagnosis was made during childhood based on characteristic clinical signs: café-au-lait spots, multiple neurofibromas, and Lisch nodules observed on fundoscopy. The patient also exhibited psychomotor delay associated with mild intellectual developmental disorder.

Starting at age 14, the patient became socially withdrawn and isolated, and began experiencing repeated episodes of clastic crises, significant irritability, and a progressive deterioration in his emotional and behavioral state, which led to his first psychiatric consultation.

The psychiatric interview revealed a depressive syndrome with attention, concentration, and memory deficits.

Initial brain MRI showed fusiform thickening of the optic nerve with variable contrast enhancement, as well as white matter signal abnormalities localized to the basal ganglia and posterior fossa. Ophthalmologic evaluation confirmed the presence of Lisch nodules, and ENT assessment revealed recurrent frontal neurofibromas, the most recent of which was surgically removed in 2022.

The diagnosis retained was a major depressive episode occurring in the context of NF1, comorbid with mild intellectual developmental disorder. The patient was started on fluoxetine 20 mg/day, leading to progressive improvement in mood and cognitive functioning.

Case 2:

Ms. F.A., a 38-year-old woman, is followed for Neurofibromatosis type 2 (NF2) with comorbid schizophrenia. Her medical history includes a past undocumented surgery for a soft tissue mass in her left arm.

Her symptoms had been evolving for seven years, with progressively worsening bilateral hearing loss, balance disturbances, and binocular diplopia, prompting a neurology consultation.

Initial neurological examination showed the patient was able to stand and walk with assistance. Romberg's sign was positive on the left, and gait was laterally unsteady toward the left, with a widened base and a decomposed turn. Cranial nerve examination revealed bilateral hearing loss without facial paralysis. The remainder of the neurological exam was unremarkable.

Dermatological examination identified a single café-au-lait spot measuring 1 cm in diameter.

Neurological analysis concluded an incomplete cerebellopontine angle syndrome based on the association of cerebellar signs and bilateral vestibular nerve involvement. Brain and spinal imaging revealed multiple meningiomas and a right cerebellopontine angle schwannoma, confirming the diagnosis of NF2.

The patient was hospitalized in neurosurgery, where she underwent a ventriculoperitoneal shunt (VPS) and tumor resection, which was complicated by peripheral facial paralysis. The latter showed improvement under corticosteroid therapy, although bilateral hearing loss persisted.

Psychiatrically, the patient had been suffering from schizophrenia for at least eight years, without structured psychiatric follow-up. The psychiatric evaluation revealed a delusional syndrome with impaired judgment. She was started on olanzapine 10 mg/day, resulting in significant clinical improvement in her psychiatric symptoms.

Discussion

1. NF1:

NF1 is the most common form, accounting for approximately 96% of cases. Its incidence is estimated at 1 in 2,700 births, while NF2 is much rarer (1 in 33,000), as is schwannomatosis (1 in 40,000). NF1 affects both sexes equally and is independent of ethnic origin. It results from mutations in the NF1 gene located on chromosome 17q11.2, which encodes neurofibromin. NF2, on the other hand, is associated with a mutation in the NF2 gene on chromosome 22, which encodes schwannomin, while schwannomatosis is linked to mutations in the SMARCB1 gene, also located on chromosome 22.

Clinically, NF1 typically manifests between ages 10 and 15, although it may appear earlier. It is characterized by cutaneous signs (café-au-lait spots, axillary/inguinal freckling), ocular signs (Lisch nodules), and neurological signs (neurofibromas) (Table 1, Figure 1). Although NF1 is generally considered a cancer predisposition syndrome, the most frequent complication in children is impairment in academic and cognitive performance, with common deficits in attention, executive functioning, language, and visuospatial abilities.

NF2, in contrast, typically appears in young adulthood (20–30 years) with nervous system tumors (schwannomas, meningiomas, spinal tumors) (Figure 2), cataracts, and skin lesions. Schwannomatosis primarily manifests as neurological pain (paresthesia, weakness, sensory disturbances) (Table 2).

Psychiatric manifestations are commonly reported in neurofibromatosis, particularly in NF1 (Table 3).

Psychiatric symptoms in NF1 are diverse and significantly more frequent than in the general population, with approximately 33% of patients experiencing moderate to severe psychiatric disorders. Numerous studies have explored this association and have identified various psychiatric conditions, notably mood disorders, anxiety disorders, and neurodevelopmental disorders (Table 4).

A large-scale study using the U.S. National Inpatient Sample (NIS) database found that 46.5% of patients with neurofibromatosis had at least one psychiatric comorbidity. Mood disorders were the most prevalent (22.1%), followed by anxiety disorders (12.2%), substance use disorders (6%), and alcohol use disorders (4.1%). Psychotic disorders such as schizophrenia were found in about 1.9% of cases, while personality disorders were seen in 1.4%.

Interestingly, female gender and minority ethnic background appeared to be protective factors against psychiatric comorbidities, whereas age was not significantly correlated. However, some studies suggest that young adults are at higher risk of developing anxiety disorders. The severity of psychiatric symptoms seems to be proportional to the perceived severity of the disease. A more severe perceived disability is often associated with increased suicidal ideation. However, no statistically significant differences were observed in hospital mortality, length of stay, or hospitalization costs.

These findings underscore the importance of a multidisciplinary approach involving neurologists, dermatologists, geneticists, psychiatrists, and psychologists to better detect, prevent, and treat psychiatric complications associated with neurofibromatosis. Early identification of these disorders enables timely intervention, which improves patients' quality of life.

In NF1, the most frequently associated comorbidities include:

1.1 Anxiety Disorders:

The link between NF1 and anxiety disorders remains unclear [3,4]. The prevalence of anxiety in NF1 patients ranges from 1.5% to 6%. In children, NF1 has been associated with various psychiatric and behavioral problems, including anxiety, depression, obsessive-compulsive symptoms, and somatic complaints [5,6]. Compared to their unaffected siblings, children with NF1 show more internalizing problems such as anxious-depressive symptoms, social withdrawal, and difficulties with social integration. However, these disorders are frequently underdiagnosed [7,8].

1.2 Mood Disorders:

Psychiatric disorders and suicidal risk are significantly more frequent in patients with NF1 compared to the general population. Although concerning, this observation still requires further confirmation by additional research. Nevertheless, self- or other-directed aggressive behaviors appear to be less common in this population [9].

1.3 Post-Traumatic Stress Disorder (PTSD):

High levels of post-traumatic stress disorder (PTSD) have been reported following the incidental announcement of an NF1 diagnosis, especially among parents of affected children [10]. Improved communication and physician awareness of the disease's characteristics, progression, and prognosis may help mitigate PTSD symptoms in patients and their families.

1.4 Neurodevelopmental Disorders:

Children with NF1 commonly experience learning difficulties. Approximately 52% have academic performance issues, with 20% showing specific learning disorders and 32% more generalized difficulties. Boys seem to be at higher risk. These children often struggle with reading, writing, spelling, mathematics, organization, and planning [11,12]. In some families, NF1 appears more commonly associated with mild intellectual developmental disorder, while more severe intellectual disability requiring specialized education is not typical of NF1 [13].

MRI studies have revealed specific brain abnormalities in NF1 patients, including increased white matter volume, enlargement of certain subcortical regions, reduced cortical thickness, and T2 hyperintensities. These findings are linked to cognitive deficits, particularly in working memory, calculation, and behavior. A pilot study showed that a home-based computerized working memory training program led to cognitive improvements and measurable changes on functional MRI.

The association between neurofibromatosis and autism spectrum disorders (ASD) is an area of active research [14]. Recent studies report ASD prevalence in NF1 children to be as high as 25%, much higher than in the general population (0.5% to 2%). Both children and adults with NF1 show significantly higher rates and severity of social dysfunction and autistic symptoms. Results also support the influence of moderators such as age, sex, and comorbid ADHD on social outcomes in NF1 [15].

As for ADHD, its prevalence among NF1 patients ranges from 33% to 49.5%, affecting both sexes equally [16,17]. These symptoms seem to involve complex alterations in cognitive processing, visuospatial abilities, and executive functioning [18], likely arising from mechanisms distinct from those seen in ADHD among non-NF1 individuals [19,20]. Some researchers suggest that impaired visual signal processing may play a role [21].

2. NF2:

While psychiatric comorbidities in NF1 have been well documented, data concerning NF2 remain scarce and often fragmented. The neurological consequences of NF2—particularly auditory, visual, vestibular impairments, and chronic pain—can cause significant psychological distress. Anxiety disorders, depressive episodes, and adjustment syndromes have been reported in these patients, although few studies have systematically evaluated these manifestations. Functional impairment, progressive sensory loss, reduced quality of life, and uncertainty regarding prognosis all contribute to notable psychological vulnerability.

2.1 Psychotic Symptoms:

Hearing loss, a cardinal symptom of NF2, has been associated with psychiatric disorders. Kraepelin [22] was the first to describe paranoid phenomena and persecutory delusions in hearing-impaired individuals. A recent meta-analysis of epidemiological studies found an increased risk of psychiatric disorders in people with hearing loss, although odds ratios remained modest. Early exposure to hearing loss appears to increase the risk of developing

schizophrenia later in life. Proposed mechanisms include social isolation and disruptions in auditory source monitoring—the ability to localize and interpret the origin of sounds [23].

Additionally, one study found that self-reported hearing loss was associated with a higher frequency of psychotic symptoms among young hearing aid users, though this correlation was not observed in older adults [24].

2.2 Anxiety and Depressive Disorders:

Depression is a particularly concerning issue in NF2. Increased suicide rates have been reported among patients with acoustic neuromas compared to the general population [25]. Furthermore, a recent study involving patient support groups found a correlation between the onset of severe post-operative headaches, depression, and suicidal ideation [26].

Thomas et al. [27] reported that individuals with hearing impairment were four times more likely to exceed clinical thresholds for anxiety and depression symptoms than the general population. Individuals with sensory loss exhibited higher rates of depression and lower quality of life compared to those without impairments [28]. Another study exploring the relationship between hearing loss and anxiety symptoms revealed that anxiety risk was significantly higher in individuals with mild hearing loss and even greater in those with moderate or severe impairment. However, the use of hearing aids did not appear to significantly reduce this risk [29].

Conclusion:

In conclusion, existing research reveals a strong comorbidity between psychiatric disorders and neurofibromatosis, suggesting the involvement of multiple underlying mechanisms. However, it remains necessary to clarify whether these psychiatric disorders are a direct expression of a multisystemic disease. To better understand the basis of this comorbidity, further studies—particularly at the genetic and neurophysiological levels—are essential. Future research should also focus on the impact of psychiatric disorders on the clinical course and quality of life of patients, in order to better tailor therapeutic strategies and improve overall patient care.

Ethical Considerations

Informed Consent:

Written informed consent was obtained from both patients for the publication of their clinical data . All identifying information has been anonymized to protect patient confidentiality.

Conflict of Interest Statement:

The authors declare that they have no conflicts of interest related to this work.

Keywords

Neurofibromatosis type 1; Neurofibromatosis type 2; Psychiatric comorbidity; Depression; Schizophrenia; Intellectual developmental disorder; Autism spectrum disorder; ADHD.

Tables

Table 1: Diagnostic Criteria for NF1 (NIH – Bethesda, 1988)

	NIH criteria for the diagnosis of neurofibromatosis type 1
1	Six or more cafe-au-lait skin macules >5 mm in prepubertal individuals and >15 mm in postpubertal individuals
2	Two or more neurofibromas of any type or one plexiform neurofibroma
3	Axillary or inguinal freckling
4	Two or more Lisch nodules
5	Optic glioma
6	Bone lesion with sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis
7	A first-degree relative (parent, sibling, or offspring) that meets NIH criteria

*The diagnosis of NF1 requires at least two of the seven NIH criteria.

doi:10.1371/journal.pone.0138386.t001

Table 2: Manchester Diagnostic Criteria for NF2 (Evans, 1992)

Manchester criteria for clinical diagnosis of neurofibromatosis type 2 (NF2)	
Primary finding	**Additional findings needed for diagnosis**
Bilateral vestibular schwannomas	None
Family history	Unilateral vestibular schwannoma or two NF2-associated lesions (meningioma, glioma, neurofibroma, schwannoma, or cataract)
Unilateral vestibular schwannoma	Two NF2-associated lesions associated with the disorder (meningioma, glioma, neurofibroma, schwannoma, or cataract)
Multiple meningiomas	Unilateral vestibular schwannoma or two other NF2-associated lesions (glioma, neurofibromas, schwannoma, or cataract)

Table 3: Psychiatric Manifestations in NF1

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References	Age/Sex	Psychiatric Disorders
Our 1st case, 2023, Morocco	36/M	Depressive disorder comorbid with mild intellectual developmental disorder
Our 2nd case, 2025, Morocco	38/F	Psychotic disorder
R. Belzeaux et al., 2006, France	54/F	Depressive disorder comorbid with intellectual developmental disorder
Vaucher and Paz, 2019, France	6/F	Anxiety disorder
Wiener et al., 2018,	21/F	Anxiety disorder
Cohen et al., 2015, France	20/M	Depressive disorder

Table 4: Genetic Determinants and Neuropsychological Impact in NF1

Aspect	**Description**
Gene	NF1 gene on chromosome 17q11.2
Protein	Neurofibromin (tumor suppressor regulating Ras proteins)
Brain abnormalities	Increased white matter volume, subcortical region enlargement, reduced cortical density, T2 hyperintensities (UBOs)
Neuropsychological consequences	Impairments in attention, memory, executive functions, language, visuospatial skills

Figures

Figure 1: Cutaneous Neurofibroma in NF1

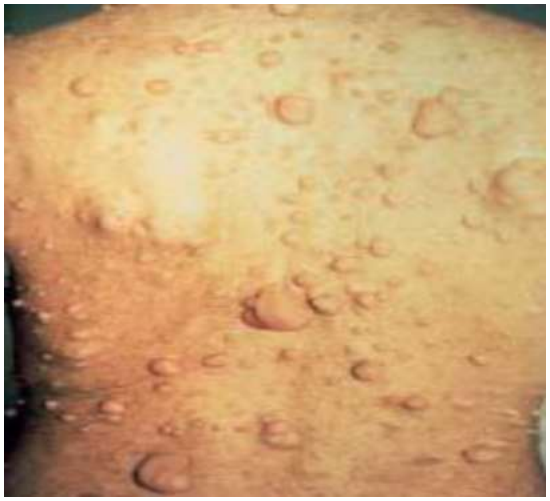
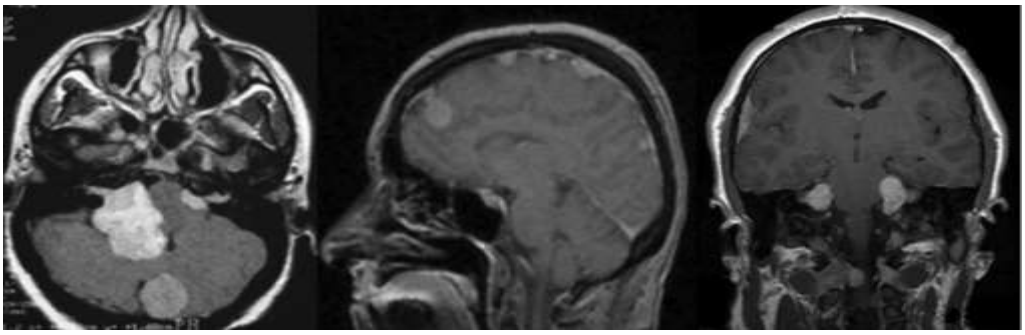


Figure 2:MRI Showing Bilateral Vestibular Schwannomas and Multiple Meningiomas in a Patient with NF2



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