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Review

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A Systematic Review of the Psychiatric Associates of Nf2-Schwannomatosis and How These Compare Against Other Neuro-Cutaneous Disorders

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Abstract

Neurofibromatosis type 2 (NF2), now called NF2-schwannomatosis is a debilitating genetic syndrome that can cause widespread physical impairment such as deafness, visual impairment, and limb weakness. The molecular and physical manifestations of NF2 have been well described, and several studies have demonstrated the negative impact of NF2 on Quality of Life (QOL). In contrast, few studies have addressed whether there are specific psychiatric associates of NF2-schwannomatosis.

This current review summarises what is known about psychiatric features associated with NF2-schwannomatosis. For comparison, the prevalence of similar features in other genetically distinct neuro-cutaneous disorders is also briefly described.

It is hoped that the information provided in this review will highlight potential areas for future research in NF2-schwannomatosis, with the subsequent aims of optimizing holistic service provision and enhancing the quality of life for patients with NF2-schwannomatosis.

Keywords: NF2 • NF2-schwannomatosis • Psychiatric

Introduction

NF2-schwannomatosis is a multiple neoplasia syndrome caused by a pathogenic variant in the NF2 tumour suppressor gene on chromosome 22q12 [1]. This site encodes the 69 kDa protein product, merlin (moesin-ezrin-radixin-like protein) [2]. Tumour formation occurs when both gene alleles are inactivated. The prevalence rate in England is estimated to be 1 in 50500, with a birth incidence of 1 in 27956 [3].

NF2-schwannomatosis is characterized by the development of vestibular schwannomas, leading to hearing loss, tinnitus, and dizziness. However, the patient may also develop schwannomas, meningiomas and spinal ependymomas throughout the nervous system, alongside pathology affecting the eye (e.g., cataract, hamartoma), and the skin [4].

These diverse physical burdens can lead to considerable neurological disability. It is therefore not surprising that NF2 has a significant negative impact on QOL [5-11]. Typically, this reduction on QOL has been associated with worsening physical health, notably with pain and deafness. A recent meta-analysis of QOL surveys performed in patients with NF2-schwannomatosis and three other genetically distinct conditions, Neurofibromatosis Type 1 (NF1), LZTR1-schwannomatosis and SMARCB1-schwannomatosis respectively demonstrated the considerable breadth of impact of these disorders on QOL, whilst also highlighting the lack of detailed large scale studies of patients with either form of schwannomatosis. Importantly, this meta-analysis also showed that psychological health is severely impacted by NF2-schwannomatosis .

To date, only one study has examined the extent of mental health disorders within an NF2-schwannomatosis sample population [21]. Typically, previous studies have been conducted using small sample sizes and as a subset of larger populations, mainly consisting of patients with NF1, LZTR1-schwannomatosis, or SMARCB1-schwannomatosis.

This is at odds with the considerable literature on other genetically distinct neurocutaneous disorders, such as Neurofibromatosis type 1, Tuberous sclerosis (TS) and Sturge Weber Syndrome (SWS). In addition, whilst the cost of the physical impact of NF2-schwannomatosis has been quantified, the economic burden of the neuropsychiatric impact of NF2-schwannomatosis has not been investigated.

What is known about the association between psychiatric disorders and NF2-schwannomatosis?

Qualitative reports and Quality of Life (QOL) studies have shown that NF2-schwannomatosis can have a significant psychological impact [5-9]. Typically, the examination of depression and anxiety symptoms has been as small scale, sub scores and as part of a broader study in a mixed patient group (combining NF1, NF2, LZTR1-schwannomatosis and SMARCB1-schwanomatosis patients). Within these studies, the levels of depression and anxiety are typically scored higher in NF2-schwannomatosis participants, relative to the general population. To date, there have been no large scale studies examining the prevalence, causation, or impact of psychiatric disorders within the NF2-schwannomatosis population. This is important because a failure to appreciate any psychiatric comorbidity, could potentially limit the capacity for optimal function.

In our opinion, to fully appreciate the impact from any such psychiatric comorbidity, it might be helpful to address the following questions.

What is the prevalence of psychiatric disorders in NF2-schwannomatosis?

Is there a relationship between the severity of psychiatric co-morbidity and the severity of the physical manifestations of NF2-schwannomatosis?

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What are the best treatment options for managing psychiatric disorders in NF2?

To date, the largest study to explore psychiatric morbidity in NF2-schwannomatosis is by Wang. This is also the only study to have examined the mental health of patients with NF1, NF2, LZTR1-schwannomatosis and SMARCB1-schwannomatosis. The authors conducted a cross sectional study (using a range of surveys), on patients with NF1 (n=133), NF2-schwannomatosis (n=94) and LZTR1/SMARCB1-schwanomatosis (n=21) respectively. The surveys used in this study included the Centre for Epidemiologic Studies Depression Scale, Perceived Stress Scale-4, Rosenberg Self Esteem Scale and State Trait Anxiety Inventory for Adults form Y2 Surveys. Each survey was completed by participants, typically within the hospital outpatient waiting area. Comparators included general population normative data. This study is unique in being the only to date, which has specifically assessed for the presence of psychiatric comorbidities, rather than factors affecting QOL.

The authors noted a significant increase in the level of anxiety and depression in NF1, NF2-schwannomatosis, and in LZTR1/SMARCB1-schwanomatosis patients, relative to the general population. No published results were given for the NF2-schwannomatosis sample alone. The authors stated that there was no significant difference between NF1, NF2 and Schwannomatosis for either males or females on any of the emotional functioning measures. Interestingly, the study also explored the association between the level of physical health (as defined by walking, hearing and facial function) and the degree of mental health impairment. The authors reported a significant relationship between worsening facial function and the level of anxiety in patients with NF2.

Wang, et al., 2012 also noted a higher number of yearly medical visits in those NF1, NF2/LZTR1/SMARCB1 Schwannomatosis patients who had higher scores on surveys for depression and anxiety, or who had higher levels of perceived stress, and lower levels of self-esteem. However, no significant association was seen in the study between walking and hearing impairment. Despite the relatively small scale of this study, it was important in showing that NF1, NF2 and LZTR1/SMARCB1-Schwannomatosis are associated with significant levels of depression and anxiety and that a component of these symptoms, may be related to facial weakness.

The burden of facial weakness in NF2 was previously noted by Patel. This informative qualitative study was conducted on 6 adult (18 years and over) NF2 patients. The team explored the psychosocial impact of NF2 on patients through open ended interviews. Although no specific attempts were made to diagnose psychiatric disorders, it provided a useful understanding of the broader narrative of the psychological impact of NF2-schwannomatosis. The team developed a framework to allow exploration of the impact that NF2 had on patients, specifically, the physical, social, and emotional impact of NF2. A thematic framework approach was used under the "Framework analysis approach", with the study identifying 3 main themes: ''Impact of the disease'', ''emotional response to the disease'' and ''awareness of NF2''. Communication difficulties were consistently noted as one of the major impacts of disease. This was largely caused by facial weakness and loss of hearing. The impact of these impairments appeared to lead to social withdrawal and behavioral avoidance, associated with embarrassment, shame, or feelings of self-consciousness. The severe impact of communication difficulties typically led participants to interact with only a close family member. This was largely due to feelings of self-consciousness when talking to friends and acquaintances. There was also notable frustration associated with the inability to express emotion (e.g. happiness through smiling), due to facial weakness.

The study also highlighted other factors limiting quality of life, including the presence of excessive fatigue and the inability to work. Participants were clearly negatively affected by the effects of NF2: Participants expressed a narrative relating to their NF2 diagnosis that included the words ''shock'', ''cry'', ''feel alone'' and ''frustrating''. They also identified emotions of embarrassment, self-consciousness, sadness, lack of control and shame, all associated with facial weakness. The apparent lack of knowledge and awareness of NF2 amongst healthcare professionals and in society in general, was also noted as a factor affecting psychological wellbeing.

A range of informative qualitative studies have also been published by Neary [6,7]. These papers highlight the broader range of difficulties facing NF2-schwannomatosis patients, with the patient narratives highlighting the emotional squeal of psychosocial and body system specific impairments [6,7].

The associated consequences of facial weakness are clearly extensive. Smith, et al 2013 examined the psychological implications that NF2 patients have concerning appearance. Specifically, sexual, bodily, and social self-consciousness resulted in raised levels of loneliness. The team examined NF1 (n=79) and NF2 (n=48) participants using the Derriford appearance scale 59 (DAS59), the Rosenberg Self Esteem Scale (RSES) and the UCLA Loneliness Scale (Shortened Version, Version 3). The results indicated that 42.2% of NF2 women had an NF2-related appearance concern. Women with NF2 had significantly higher levels of social self-consciousness of appearance in comparison with general population norms.

There are limited published studies investigating treatment interventions to reduce the psychological impact of NF2-schwannomatosis. Several studies are orientated around a novel psychological intervention for NF2-schwannomatosis patients with severe hearing impairment or deafness, used in one NF2 center within the USA.

Funes, et al., 2019 previously noted the impact of hearing loss in the mental health of their patients. They created a "Mind Body program" (Relaxation Response and Resiliency Program for Deaf NF2, d3RP-NF2) specifically to help treat NF2 patients with significant or complete hearing loss. The purpose of the program was to build emotional resilience through teaching deep breathing and mind mapping awareness. The intervention also used mindfulness, adaptive thinking, and growth enhancement through positive psychological concepts. During the study, the team performed the intervention in a randomized control format. The control arm of the study was usual psychological care (Health Enhancement Program). Both programs were conducted online over an 8 week period. A trained clinical psychologist led each session. The program was assisted by a Communication Assisted Real Time Translation (CART), which allowed a text report of all verbal communication. Carter, et al., 2021 examined the effect of the Relaxation Response and Resiliency Program for Deaf NF2, d3RP-NF2 intervention in reducing perceived stress and depression within this sample. The PHQ-9 was used to assess depression and the PSS-10 was used as a measurement of perceived stress. 45 participants were randomly allocated to each intervention. The team noted a higher baseline level of depression (PHQ-9) and perceived stress (PSS-10) in NF2 participants. The d3RP-NF2 group demonstrated significant (but not clinically significant) reduction in depression and perceived stress between baseline and post-test. This was sustained 6 months post intervention. Standard treatment (Health Enhancement Program) did not show any significant difference 6 months post intervention. No significant difference was noted between groups at the 6 month follow up point. This study indicates the overall need for further research into meaningful treatment options for NF2-schwannomatosis patients. This is particularly true for those with severe hearing impairment or deafness and facial weakness and associated communication problems.

To date, there have been no studies investigating medication treatment for psychiatric disorders in NF2-schwannomatosis patients. There are also no studies examining the effects of NF2 on cognition.

Psychiatric Disorders Found in other Neurocutaneous Syndrome

Neurofibromatosis Type 1 (NF1)

Neurofibromatosis type 1 (NF1) is caused by a pathogenic variant in the NF1 gene at chromosome 17q11.2. This encodes a protein known as Neurofibromas. Common physical manifestations include the presence of Neurofibromas (sporadic tumors) across the body, pigmentary abnormalities (café au lait macules), gliomas, musculoskeletal abnormalities, and gastrointestinal abnormalities.

The prevalence of NF1 is approximately 1:3000-4000. Psychiatric disorders are found at higher prevalence in NF1 patients. It is well documented that NF1 is associated with higher levels of cognitive dysfunction and neurodevelopmental disorders in children. Specifically, children are known to have higher rates of neuro-developmental conditions. Hofman, et al., 1994 found that at least 30% of their patients with NF1 could be classified as having ADHD, Autism Spectrum Disorder (ASD), estimated to be 4-5 times the general population norms. There is also an increased prevalence of depressive disorders which can be as high as 55% in some NF1 samples. NF1 patients have been shown to exhibit impairments in social, reading, spelling and mathematics abilities.

Tuberous Sclerosis (TSC)

Tuberous Sclerosis (also known as Tuberous Sclerosis Complex) is a multisystem disorder commonly affecting the brain, kidneys, heart, eyes, and lungs. Benign tumour growth at these sites is caused by a pathogenic variant in the TSC1 or TSC2 genes. The estimated prevalence of tuberous sclerosis is 6•8 –12•4 per 100000 people. Despite the physical symptoms, it is now well established that TSC patients are affected by behavioral, psychiatric, intellectual, neuropsychological, and psychosocial difficulties. Interestingly, in 2003 an international consensus panel developed guidelines for the inclusion of neuropsychiatric evaluations of TSC patients as part of routine assessments and reviews. This was based on growing evidence of neuropsychiatric comorbidities affecting TSC patients.

The most common psychiatric disorders observed in association with TSC include neurodevelopmental disorders such as autism spectrum disorders (25%–50%) and attention deficit hyperactivity disorder (ADHD, 30%–50%). The prevalence of ADHD therefore being up to 10 times more prevalent in patients with TSC, than in the general population. Depression and anxiety disorders appear raised at 26%-35% and 28%-59% respectively. In TSC, approximately 50% of individuals have an IQ score of less than 70 and therefore have intellectual disability, ranging from mild or moderate to profoundly impaired. Population based studies have identified that as many as 30% of individuals with TSC fall in the profoundly impaired range.

Sturge Weber Syndrome (SWS)

SWS is a rare neurocutaneous syndrome characterized by capillary malformation (or port-wine birthmark) in the ophthalmic distribution of the trigeminal nerve, vascular malformations, glaucoma, and a leptomeningeal angioma. The estimated incidence rate is between 1:20-50,000 live births.

A limited number of studies have been published on the neuropsychiatric associates of SWS. These are mainly case studies, alongside one small cross-sectional survey. Turin, et al., 2010 undertook a survey of 16 patients with SWS (aged between 3 and 34 years) [48]. The team noted an increased prevalence of substance misuse (67%). Other disorders shown to be more prevalent relative to general population were mood disorders (31%), disruptive behavior disorder (25%), and adjustment disorder (25%).

`Gadit, et al., 2011 reported the case of a 22 year old male with SWS and psychosis, treated with antipsychotic medication. The authors wished to highlight the need for good communication between neurology and psychiatry departments. Madaan, et al., 2006 also presented a case of an 82 year old patient admitted to a psychiatric inpatient unit with odd behaviour ("episodic angry slapping").

Discussion

As with NF2, evidence from the SWS literature appears to indicate the need for a large scale study to determine the prevalence rates of psychiatric disorders.

Conclusion

Currently, there are relatively few studies which have reported on the psychiatric disorders in patients with NF2-schwannomatosis. It is hoped that this review will help demonstrate the need for detailed and larger scale studies in NF2-schwannomatosis sample populations. Furthermore, an evidence base regarding effective psychiatric treatment may also be of use. It is hoped that the QOL and economic burden associated with NF2-schwannomatosis can be improved through greater awareness of potential neuropsychiatric conditions, co-morbid with NF2-schwannomatosis.

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