

## **Pediatric Patients with Neurofibromatosis Type 1 and its Association with Intellectual Impairment**

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### **ABSTRACT**

Today Neurofibromatosis type 1 belongs to a genetic disorder in which there is a mutation of a gene that is on chromosome 17 which will cause at some point in the patient's life the development and growth of tumors in the central nervous system or even outside it. Epidemiologically it is known that there is no predilection for sex or person, but it is known and common, that the onset of presentation of symptoms is given after birth, for this reason, it is a disorder that occurs more frequently in children, it is important to recognize the disorder to be able to attend to the complications that occur with the evolution of the disease, remembering that a specific treatment is not known exactly. It is considered necessary the integral attention to the multiple complications that could come present, which mentions some of the most serious are: Musculoskeletal disorders, as well as presenting skin problems, being frequent presentation in the first year of life. Eye problems, learning problems at school age and even worse prognosis can reach a degree of mental retardation.

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### **INTRODUCTION**

There are genetic disorders in which the cells of the nervous system are affected, as well as their growth and development. They reach such a degree that it favors the development of tumors that grow on the nerves and manage to produce certain accompanying abnormalities such as stains on the skin of coffee with milk and deformities in bones.

This entity and its encompassed symptomatology have been known as neurofibromatosis, where it has been classified into 2 types (type 1 and type 2) due to the affected chromosomes involved in its development such are 17 and 22 respectively. Type 1 is the most common variant reaching an incidence of up to 1 in 4000 people in the US. Only 30 to 50% of cases have a history of the pathology, while the rest are usually due to genetic mutations *Novo*, which favor its appearance, and from there, it can be inherited to consecutive generations.

NF1 is also known as *von\_Recklinghausen's disease* or peripheral neurofibromatosis, due to the clinical characteristics it usually encompasses, in peripheral areas of

The body, although it is no longer recognized as such due to the potential of the disease to produce tumors in the CNS.

The clinic with which patients usually study ranges from the appearance of *café-au-lait spots* on the skin, or the development and growth of subcutaneous neurofibromas with different evolution times.

Also, the implications of this disease with the appearance or development of psychiatric disorders in young patients suffering from it have been described, such as autism disorder or hyperactivity with attention deficiency, or clinical alterations depending on the place where a tumor with the origin of nervous tissue has originated.

In this research work, important points will be exposed in which NF1 has been associated in the same way with cognitive alterations in the childhood stage, as well as aspects in its etiology, possible causes and clinical characteristics that these patients usually develop in the young stage.

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### THEORETICAL FRAMEWORK

Neurofibromatosis type 1 (NF1), also known as Hausen von Reckling disease, is a multisystem disease that affects the growth cells of nerve tissue, in addition to a set of rare diseases of genetic cause (a tumor suppressor gene, on chromosome 17) that are characterized by the development of multiple benign tumors in the nerves of the body and skin; as well as the formation of spots. It has a prevalence of 1 in 3000 children. Some of the complications that this disease has are learning problem, mental retardation, short stature, due especially to deformities in the spine, scoliosis, macrocephaly, optic glioma, brain tumors, and tumors in the spine, and chronic constipation.

The most frequent complications in childhood are deficits of cognition and behavior however other children with this pathology are at high risk of developing other more serious physical complications that can affect virtually any system of the body, these include disfiguring plexiform neurofibromas, scoliosis, pseudoarthrosis and optic nerve gliomas. Unfortunately, what makes it difficult for the pathology to be fully known is that the variety and variability of the problems or presentations that we may have of the disease are very extensive.

It is a disease that results from a single genetic mutation of the neurofibromin gene that codes for NF1 "genetic mutations are more likely to affect cognitive processes", which is involved in both growth regulation and development, among other characteristics such as skeletal problems and abnormalities, in addition to cognitive functionalities such as learning and attention problems. That it is worth highlighting the last two as a complication of this disease in children. Evidence of deterioration was found in all academic areas such as word reading, comprehension, mathematics, and spelling. 60% of children have these complications. In other words, all children have been observed to have a cognitive impairment such as specific learning disabilities, such as developmental dyslexia and development dyscalculia, visuospatial, orientation and attention deficit, language acquisition, and spatial memory.

Several genetic syndromes exhibit specific learning disabilities. Along with NF1, Turner, fragile X, and Velocardiofacial syndromes are the most studied. According to this approach, dyscalculia development is considered a congenital and persistent disability in achieving the normal levels of arithmetic skills that arise when the specialized number system does not develop normally with corresponding deleterious effects on the acquisition of higher-level mathematical skills. Neuroimaging studies of neuronal bases of dyscalculia development describe activations related to low numbers in the intraparietal groove (an area dedicated to numerical processing) and recruitment of the most distributed brain regions (possibly as a consequence of compensation strategies).

On the other hand, it is considered that there is a congenital and persistent disability in reading and comprehension and shows deficiencies in phonological processing, knowledge of the structure of word sounds and, in some cases, a more fundamental deficit in rapid auditory processing. Neuroimaging studies of developmental dyslexia neuronal bases describe a reactivation in the left hemisphere inferior frontal gyrus and temporoparietal cortex (underlying poor phonological processing) and word-forming visual area in the occipitotemporal region of the left hemisphere (important in word recognition). The inferior frontal white matter decreases in the left frontal and parietal parts of the arcuate fasciculus and other left perisylvian areas have also been associated with the disorder.

According to the diagnostic criteria for specific learning disorders proposed in the Diagnostic and Statistical Manual of Mental Disorders children.

It is now known that cognitive difficulties can be observed as early as two or three years of age. But a recent study revealed that difficulties occur more often in older children than in younger children. Some of the ages they took were between 2-6 years.

Regarding psychosocial functioning, higher levels of attention problems have been reported in children with NF1 than in other diseases, since they had diagnostic criteria of attentatedeficit/hyperactivity up to almost half of the patients currently studied. In addition, it has been related to an autism spectrum that is a generalized bebehavioural disorder, characterized by a marked deficit in social relationships, and repetitbehaviours with an onset in early childhood. It is considered to have a broad genetic relationship with a ratio rate between homozygous twins of up to 90%. However, there is a wide heterogeneity amongn the possible genes that cause the disease, calculating around 1000 suspicious genes. Recent studies have shown that it has a broad correlation with other genetic abnormalities, including neurofibromatosis type 1 which was shown to have autism spectrum data at some level.

It is important to mention that foe diagnosis of this pathology can be done by certain coffee spots present on the skin, as well as deformities in the spine by radiological images. In addition, they may be accompanied by neurological symptoms such as sensory or motor alterations. The studies that were used were measures such as differential capacity scales, second edition first years of form was administered to assess cognitive functioning, Digit Span Forward measures and Early Concepts of Numbers.

The procedures were carried out through genetic studies primarily as the mutation of the neurofibromin gene was required.

Among the cases found were some patterns that most often tended to present children with NF1, which was nonverbal

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reasoning, and motor development. So it shows a significant relevance among the subtests of non-verbal reasoning.

Certain scales that study these patients are but are not limited to: Social Skills Rating System, the Child Behavior Checklist, the Social Responsiveness Scale, the Behavior Rating Inventory Executive Functioning and the Dysexecutive Questionnaire. In these patients, a decrease in grey matter was found in the middle region of the frontal and parietal lobes, and an increase in total white matter. There were social and attention problems, autistic mannerisms, increased putamen and poor executive function, this decrease in grey matter together with the increase in white matter explains or was related to greater social problems, although the factor that had the greatest association with social problems was a decrease in grey matter in the precentral turn. GABA levels in patients were reduced in the medial frontal and occipital cortex, compared to controls. Glutamate + glutamine levels were normal, which points to an abnormal balance of inhibition/excitation in NF1. Medial frontal GABA levels correlate with intellectual capacity and inhibitory control.

Interestingly, NF1 patients present a reverse pattern, with higher GABA being associated with faster responses (Ribeiro et al., 2015). In this context, recent evidence supports the view that tonic GABA modulation is essential for LTP-like changes such as plastic, for example, within the motor cortex (M1), and further pharmacological studies have shown that the GABA-agonist medication could suppress M1 plasticity and learning in healthy individuals.

Since the underlying mechanisms of the disease are evident from birth, it can be speculated that they have also adapted to their deficits in acquiring skills at a behavioural level, relevant in daily life.

Cognitive impairment in NF1 has important consequences in daily life, including significant deficits in school skills, which can occur in 75% of patients with NF1 (Creajiente et al., 2008).

Impairment in working memory and executive functions is a common feature of NF1 and may be an underlying contributing factor to impairment in academic skills (Hyman et al., 2005; Crispy et al, 2008; Rowbotham et al., 2009).

Working memory is heavily involved in academic skills such as reading, writing, and arithmetic (Baddeley, 2003; Geary, 2011).

As stated before, working memory is a dopamine-mediated function. Dopamine homeostasis contributes to learning, memory and attention, however, the mechanisms by which NF1 modulates dopamine signalling are still unknown (Diggs-Andrews and Gutmann, 2013). Therefore, in a multilevel perspective, the COMT genotype (neurobiological level) could modulate working memory (cognitive level) and reflect low academic performance (functional level).

To date, we have found no studies investigating the association of this specific genetic polymorphism with cognitive performance in an NF1 population. In two different animal models of NF1, an inverse relationship between reduced dopamine levels and spatial learning impairments was observed (Anastasaki et al., 2015) suggesting the importance of NF1 dopamine activity cognition.

Neurofibromin has been shown to modulate inhibitory networks in the prefrontal and striatum regions, affecting working memory performance (Shilyansky et al., 2010), but our results suggest that variability in cognitive-level expression among NF1 individuals may occur as a result of variability in their genetic background.

It has been hypothesized that genetic modifiers could interact at a more functional level to exacerbate or compensate for signalling changes caused by the loss of NF1 (Shilyansky et al., 2010). More studies are needed to show whether NF1 can moderate the known effects of other specific genetic polymorphisms on cognition.

### DISCUSSION

Based on the knowledge acquired through the review of the bibliographic sources used to carry out this work, we have concluded that there is a close relationship between neurofibromatosis type 1 and cognitive, intellectual and developmental disorders with a variable presentation severity. It should be noted that although in numerous studies the association between these disorders has been observed, it has not been possible to establish the origin of it, since we know that neurofibromatosis type 1 is a common neurocutaneous disorder whose genetics have already been described in other reviews, however, cognitive alterations are not present in all patients who present the disease, leaving a parenthesis between the association of the two disorders. This parenthesis has been tried to complete with unproven genetic theories, the most accepted of them establishes that given the great allelic and genetic variability presented by both diseases, there may be a simultaneous and unstudied genetic alteration that affects genes that participate in cognitive development and may be modified fortuitously by genetic inheritance of the patient. Within the possible origin of the association between these two pathologies (Zimerman et al.) establishes in their study that patients with NF type 1 have a deficit in inhibition by GABA at the cortical level in the primary motor area, striated nucleus and campus that generates in these patients motor deficit and working memory. In a previous study (Hyman et al.) pointed out that cognitive and learning problems are very common in patients with type 1 NF, hindering school performance in up to 80% of the children analyzed in their sample. Of the most viewed alterations in pediatric patients with NF type1 (Rodríguez et al.) states in its study with 239 patients with the disease that was observed: Learning difficulties in 104 patients (43.5%).

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Intellectual disability in 7 patients (2.9%). Autism spectrum disorders in 10 patients (41%) and Attention deficit hyperactivity disorder in 55 patients (23%). However, in this study neuroimaging tests are not performed to determine which were brain areas involved in this dysfunction, while in the study carried out by (Castillo, Pérez and Reigosa, 2014), neuroimaging tests are performed on the 46 participants, denoting the following abnormalities: activations related to low numbers in the intraparietal grooves (an area dedicated to numerical processing) and the recruitment of brain regions more distributed (possibly as a consequence of compensation strategies) and inactivation in the lower left hemisphere, frontal gyrus and temporoparietal cortex (poor phonological processing) and visual area in the occipitotemporal region of the left hemisphere (important in word recognition) The inferior frontal white matter decreases in the left frontal and parietal parts of the arcuate fasciculus and other left perisylvian areas also involved in the disorder. Although there is no conclusive study that establishes the reason or origin of the association between NF type 1 and cognitive impairments seen in a large part of patients, the studies carried out so far can give us an introduction to the genesis of these disorders and above all open the door to genetic research to establish the genes involved in the association and this how to offer therapeutic measures that improve the quality of life of these patients.

### CONCLUSION

There is a high prevalence of cognitive deficits and neuropsychological disorders in patients with NF1. It is known that there is this relationship already described in the literature where they are mentioned as severe complications presented. We conclude that there is indeed a close relationship, which unfortunately the exact mechanism by which this association is present is not yet known, however in the literature review we find multiple authors who affirm that without having the physiopathological mechanism established, they have observed cognitive deficit in multiple patients. Therefore, we consider it important to address neurocognitive alterations. However, we understand the difficulty of clinical diagnosis of NF1 at an early age remains difficult. Although the need or not for complementary studies in asymptomatic patients is discussed. While parents often detect some difficulties, others have been observed to be underestimated. For this reason, based on the results of this study, we believe it is convenient that all patients with NF1 have an evaluation of their cognitive profile to detect what difficulties exist in each case. A correct diagnosis allows us to define the treatments that each child needs, contributing to reducing symptoms and improving the quality of life of our patients, to avoid problems. Learning problems are the most devastating symptom of the lives of those affected which contribute to a low personal image, and school deficiencies. These learning deficiencies must be attacked from an early

age, through treatments with individual psychological assessment and total family support, to prevent personal, social and economic problems such as low self-esteem, irregular academic training, and school dropout, among others. So it is convenient that patients have earlier care to reduce complications.

### REFERENCES

- I. Papadakis A. Maxine, Stephen J. Mcphee. Current. cmdt. Medical diagnosis and treatment. Ed. el Sevier. Editorial McGraw-Hill. 2015.
- II. A. Duat Rodríguez, G.Á. Martos Moreno, Y. Martín Santo-Domingo, A. Hernández Martín, J.M. Espejo-Saavedra Roca, M.L. Ruiz-Falcó Rojas, J. Argente. Phenotypic and genetic features in neurofibromatosis type 1 in children. *An Pediatr (Barc)*. 2015; 83(3):173-182.
- III. huijbregts s, outfielder m, rombouts s, swaab h, verbist b, arkinck e et al. cerebral volumetric abnormalities in neurofibromatosis type 1: associations with parent ratings of social and attention problems, executive dysfunction, and autistic mannerisms. *Journal of neurodevelopmental disorders*. 2015; 7(1).
- IV. Bonita P. Klein-Tasman, Kelly M. Janke , Wen Luo , Christy L. Casnar , Scott J. Hunter , James Tongsgard , Pamela Trapanè , Faye van der Fluit , and Lorri A. Kais. Cognitive and Psychosocial Phenotype of Young Children with Neurofibromatosis-1. *J Int Neuropsychol Soc*. 2014; 20(1): 88–98.
- V. Miladys Orraca-Castillo, Nancy Estévez-Pérez and Vivian Reigosa-Crespo. Neurocognitive profiles of learning disabled children with neurofibromatosis type 1. *Frontiers in Human Neuroscience* 2014; 8: 386.
- VI. Goldsmith A. Lowell, Gilchrest, Paller, Leffell, Wolf. Fitzpatrick. *Dermatology in General Medicine*. Ed. 8th. Editorial Médica Panamericana. 2014.
- VII. Shruti Garg, MRCPsych, Jonathan Green, FRCPsych, Kathy Leadbitter, PhD, Richard Emsley, PhD, Annukka Lehtonen, DPhil, PhD, D. Gareth Evans, MD, FRCP, and Susan M. Huson, MD, FRCP. Neurofibromatosis Type 1 and Autism Spectrum Disorder. *Pediatrics* 2013; 132: e1642–e164.
- VIII. Zhao X, Li J, Shi L, Yang L, Wu Z, Zhang D. Surgical Treatment of Dystrophic Spinal Curves Caused by Neurofibromatosis Type 1. *MD Journal*. 2016; 95(14):1-5.
- IX. shruti garg, annukka lehtonen, susan m huson, richard emsley, dorothy trump, d gareth evans, jonathan green. *Autism and other psychiatric*

## Pediatric Patients with Neurofibromatosis Type 1 and its Association with Intellectual Impairment

- comorbidity in neurofibromatosis type 1: evidence from a population-based study. *Developmental Medicine & Child Neurology* 2013; 55: 139–145.
- X. lehtonen a, howie e, trump d, huson s. behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. *Developmental medicine & child neurology*. 2012; 55(2):111-125.
- XI. Author Yon Albus. *Atlas of Pediatric Dermatology*. Ed. 2nd. Editorial Océano Ergon.2009.
- XII. Máximo Zimerman, MaximilianJ.Wessel, Jan E. Timmermann, SofiaGranström, Christian Gerloff, Victor F. Mautner, Friedhelm C. Hummel. Impairment of Procedural Learning and Motor Intracortical Inhibition in Neurofibromatosis Type 1 Patients. *EBioMedicine* 2 (2015); 1430–1437.
- XIII. Danielle de Souza Costa, Jonas J. de Paula, Antonio M. Alvim-Soares Jr, Patrícia A. Pereira, Leandro F. Malloy-Diniz, Luiz O. C. Rodríguez, Marco A. Romano-Silva and Débora M. de Miranda. COMT Val 158 Met Polymorphism Is Associated with Verbal Working Memory in Neurofibromatosis Type 1. *Frontiers in Human Neuroscience* 2016; 10: 334.