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# Neuropsychological performance in neurofibromatosis type 1☆

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**Abstract**
*Introduction:* Neurofibromatosis type 1 (NF1) is a genetic disorder with various clinical manifestations that affect the peripheral and central nervous system, as well as the skin, bones and endocrine and vascular system. There is still insufficient knowledge of neuropsychological effects of NF1 on children, and there is some controversy about the cognitive deficits that defines the cognitive profile of patients affected by this disorder.
*Aims:* In this study an analysis is made of the neuropsychological performance of a group of patients affected by NF1, compared with a control group of healthy children.
*Subjects and method:* A comparison was made between the neuropsychological performance of a group of 23 boys and girls with a mean age of 8.7 years (+/−1.39) and diagnosed with NF1, and a control group consisting of 21 healthy children, with mean age of 8.9 years (+/−1.41) and with similar socio-demographic characteristics. The Wechsler Intelligence Scale for Children (WISC) was applied to evaluate the subjects of both groups.
*Results:* The group of patients affected with NF1 showed a lower performance in every primary index of WISC IV: Verbal Comprehension Index, Fluid Reasoning Index, Working Memory Index, Processing Speed Index, and full scale IQ. Only in two subscales were no statistically significant differences observed: similarities and coding.
*Conclusion:* The results show subtle and generalised neuropsychological alterations in the sample of children affected with NF1, which affect most of cognitive domains that have been evaluated. Proper specific and early neuropsychological treatment should be provided in order to prevent the high risk for these children of presenting learning difficulties and school failure.


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**PALABRAS CLAVE**
Cociente intelectual;
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Rendimiento neuropsicológico;
Escala de inteligencia de Wechsler para niños-IV

**Rendimiento neuropsicológico en la neurofibromatosis tipo 1**

**Resumen**
*Introducción:* La neurofibromatosis tipo 1 (NF1) es un trastorno genético con manifestaciones clínicas muy variables que pueden expresarse en el sistema nervioso central y periférico, así como en piel, hueso, sistema endocrinológico y vascular. Los aspectos neuropsicológicos de la NF1 en la infancia continúan sin ser suficientemente conocidos, existiendo controversia acerca de los posibles déficits que definen el perfil cognitivo de estos niños.
*Objetivo:* Estudiar el rendimiento neuropsicológico de un grupo de pacientes con NF1 en comparación con un grupo de control de niños sanos.
*Sujetos y método:* Se estudia el rendimiento neuropsicológico de un grupo de 23 niños y niñas con diagnóstico de NF1, con una edad media de 8,7 años ± 1,39 comparado con otro grupo formado por 21 niños sanos con una edad media de 8,9 años ± 1,41 con características sociodemográficas similares. A todos los sujetos se les aplicó la Escala de Inteligencia de Wechsler infantil (WISC-IV).
*Resultados:* Se observa en el grupo con NF1 un rendimiento menor que el grupo control en los índices globales del WISC-IV: comprensión verbal, razonamiento perceptivo, memoria de trabajo, velocidad de procesamiento y cociente intelectual global. Únicamente en los subtest de claves y semejanzas no se han apreciado diferencias estadísticamente significativas entre ambos grupos.
*Conclusión:* Los resultados reflejan la existencia de alteraciones neurocognitivas sutiles y generalizadas en la muestra de niños con NF1, que afectan a la mayoría de los dominios cognitivos evaluados. Se subraya la necesidad de que reciban una atención neuropsicológica específica precoz para prevenir el mayor riesgo de presentar dificultades de aprendizaje y fracaso escolar.


## Introduction

Neurofibromatosis (NF) is a hereditary autosomal dominant disease with a variable expression, although half of the cases result from de novo mutations. It affects the tissues that support the central and peripheral nervous systems. It is a neurocutaneous disorder that causes changes in skin pigmentation (''café au lait'' macules), the cranial nerves and the spinal cord. It can also manifest with additional features, such as neurofibromas (cutaneous, subcutaneous or intraspinal tumours), pain in affected nerves, epileptic seizures, blindness or deafness secondary to gliomas in the optic or vesticulocochlear nerves, or hydrocephalus due to aqueductal stenosis.

There are two distinct forms of NF based on clinical, genetic and pathophysiological features, both of which belong to the broader category of neurocutaneous syndromes or phakomatoses. One is the peripheral form, known as NF type 1 (NF1), formerly von Recklinghausen disease. The other is the central form, also known as NF type 2 (NF2).[1] Like NF1, it is a hereditary autosomal dominant disease, which in this case is caused by a gene located in chromosome 22q21.

The incidence of NF1 is of 1 per 3000–4000 individuals. The disease is caused by mutations in the *NF1* gene located in chromosome 17q11.2. Approximately half of the cases are de novo mutations.[2] The clinical diagnosis of NF1 requires the presence of at least 2 of the criteria established at the National Institute of Health Consensus Development Conference[3] held in 1988 (Table 1).

**Table 1** Diagnostic criteria for neurofibromatosis type 1.

*The individual must present with 2 or more of the following:*
1. Six or more ''cafe au lait'' macules.
   Over 0.5 mm in greatest diameter in prepubertal children
   Over 1.5 cm in greatest diameter in postpubertal children
2. Two or more neurofibroma of any type or one plexiform neurofibroma
3. Freckling in the axillary and/or inguinal regions
4. Optic pathway glioma
5. Two or more Lisch modules (benign iris hamartomas)
6. A distinctive osseous lesion
   Sphenoid dysplasia
   Dysplasia or thinning of the long bone cortex with or without pseudarthrosis
7. A first-degree relative with NF1

*Source*: National Health Institute.[3]

Neurofibromatosis type 1 can affect early developmental processes, increasing the risk of learning difficulties in childhood. Approximately 80% of children with NF1 have cognitive comorbidities, with marked impairment in one or more cognitive functions, which has a negative impact on academic achievement and quality of life. In the past, these children received diagnoses of mental retardation, but more recent studies have confirmed that only 4%–8% of individuals with