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ORIGINAL ARTICLE

Phenotypic and genetic features in neurofibromatosis type 1 in children☆

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KEYWORDS
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Abstract
Introduction: Neurofibromatosis type 1 (NF1) is the most common neurocutaneous disease, nevertheless the number of publications providing clinical and genetic data from a significant number of children is limited.
Material and methods: The available clinical, epidemiological, radiological and genetic data from 239 children with NF1, who attended at a specialist NF1 clinic between January 2011 and December 2013 were recorded.
Results: All the 239 patients had a clinical and/or genetic diagnosis of NF1. The mean age at diagnosis was 2.65 ± 2.85 years. In our series 99.6% met the diagnostic criteria of *café au lait* spots, 93.7% those of axillary and inguinal freckling, 7.1% showed typical bone lesion, 38.1% neurofibromas, 23% plexiform neurofibromas, 31.4% optic pathway glioma, Lisch nodules were present in 43.1%, and 28% patients had a first degree relative affected with NF1. The *NF1* genetic study was performed in 86 patients, and a description of the gene mutations found in 72 of them is presented. Furthermore, other clinical data previously associated with NF1, either because of their frequency or their severity, are detailed.

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Conclusions: The difficulty for clinical diagnosis of NF1 early ages is still evident. Although, the need for further studies in asymptomatic patients is discussed, cranial MRI in children with NF1 may be helpful in the clinical diagnosis, given the high frequency of optic glioma observed in this cohort.

PALABRAS CLAVE
Neurofibromatosis tipo 1;
Gen *NF1*;
Glioma óptico;
Neurofibromas;
Ras/MAPK

Características fenotípicas y genéticas en laneurofibromatosis tipo 1 en edad pediátrica

Resumen
Introducción: La neurofibromatosis tipo 1 (NF1) es la enfermedad neurocutánea más frecuente, pero el número de trabajos en que se recogen los datos clínicos y genéticos de un número amplio de niños es escaso.
Material y métodos: Se recogen los datos clínicos, epidemiológicos, radiológicos y genéticos disponibles de 239 niños con NF1, atendidos en la consulta monográfica de NF1 entre enero del 2011 y diciembre del 2013.
Resultados: Doscientos treinta y nueve pacientes tenían un diagnóstico clínico y/o genético de NF1. La edad media al diagnóstico fue de $2{,}65 \pm 2{,}85$ años. Cumplían los siguientes criterios diagnósticos: 99,6% manchas café con leche; 93,7% efélides axilares e inguinales; 7,1% lesión ósea característica; 38,1% neurofibromas, un 23% presentaron neurofibromas plexiformes; 31,4% glioma de vía óptica; 43,1% nódulos de Lisch, y un 28% tenían un familiar de primer grado afecto de NF1. En 86 pacientes se realizó el estudio genético de *NF1*. Se describen las mutaciones encontradas en 72 pacientes. Además, se detallan otros datos clínicos, que, ya por su frecuencia, ya por su gravedad, han sido asociados a NF1.
Conclusiones: La dificultad del diagnóstico clínico de la NF1 en edades precoces sigue siendo patente. A pesar de que se discute la necesidad o no de estudios complementarios en pacientes asintomáticos, la resonancia magnética craneal en niños con NF1 puede ser de gran ayuda en el diagnóstico clínico dada la alta incidencia del glioma de vía óptica que observamos en nuestra serie.

Introduction

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is a genetic disorder that primarily involves the skin and the nervous system, characterised by the presence of café-au-lait macules (CALMs), axillary and inguinal freckling, iris Lisch nodules, cutaneous neurofibromas and a higher-than-average risk of tumour development. Its clinical expression is heterogeneous, even within a single family, and its morbidity and mortality are associated with multisystemic complications.[1,2] Although it is the most prevalent neurocutaneous disorder, few studies have collected the clinical and genetic data of a broad number of children with NF1. Most reviews retrieve the data from the same studies, mainly from those conducted by Huson in south-east Wales in 1988 and 1989, but the proportion of children in these studies was low.[3–5] The largest study focusing on the paediatric population that we found in the literature is the one conducted by Boulanger and Larbrisseau[6] in 2005. There have been significant advances in the understanding of its genetic basis. However, genetic studies include few clinical data, and phenotypic studies, most of which were conducted long ago, do not include genetic data. Our aim was to provide an exhaustive phenotypical description in a broad sample of paediatric patients with NF1 along with all the available molecular data.

Materials and methods

We conducted a descriptive, cross-sectional, observational retrospective study. We collected the clinical, epidemiological, radiological and genetic data available for every patient 0–18 years of age that received care at a specialist neurofibromatosis clinic between January 2011 and December 2013 and met the clinical diagnostic criteria for NF1 established by the National Institute of Health of the United States[7] (Table 1) or with a genetic diagnosis of NF1. The diagnosis of neurofibromatosis-Noonan syndrome (NFNS) required that the patient also met the clinical criteria for Noonan syndrome proposed by van der Burgt[8] (Table 2).

Results

We analysed the data of 332 patients, of which 239 children from 225 families met the inclusion criteria; 14 children had either siblings or cousins that were included in the sample.