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High frequencies of plexiform neurofibromas, mental retardation, learning difficulties, and scoliosis in Brazilian patients with neurofibromatosis type 1

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Abstract

A clinical study of Brazilian patients with neurofibromatosis type 1 (NF1) was performed in a multidisciplinary Neurofibromatosis Program called CEPAN (Center of Research and Service in Neurofibromatosis). Among 55 patients (60% females, 40% males) who met the NIH criteria for the diagnosis of NF1, 98% had more than six café-au-lait patches, 94.5% had axillary freckling, 45% had inguinal freckling, and 87.5% had Lisch nodules. Cutaneous neurofibromas were observed in 96%, and 40% presented plexiform neurofibromas. A positive family history of NF1 was found in 60%, and mental retardation occurred in 35%. Some degree of scoliosis was noted in 49%, 51% had macrocephaly, 40% had short stature, 76% had learning difficulties, and 2% had optic gliomas. Unexpectedly high frequencies of plexiform neurofibromas, mental retardation, learning difficulties, and scoliosis were observed, probably reflecting the detailed clinical analysis methods adopted by the Neurofibromatosis Program. These same patients were screened for mutations in the GAP-related domain/GRD (exons 20-27a) by single-strand conformation polymorphism. Four different mutations (Q1189X, 3525-3526delAA, E1356G, c.4111-1G>A) and four polymorphisms (c.3315-27G>A, V1146I, V1317A, c.4514+11C>G) were identified. These data were recently published.

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- Plexiform neurofibroma
- Mental retardation
- Learning difficulties
- Scoliosis

Introduction

Neurofibromatosis type 1 [NF1; online Mendelian inheritance in man (OMIM 162200)] is a common autosomal dominant genetic disorder with an incidence of approximately 1 in 3,000. It is characterized by multiple café-au-lait spots, freckling, Lisch nodules, multiple skin neurofibromas, skeletal dysplasia, and optic gliomas (1). Learning disabilities have also been observed in patients with different inactivating mutations

and even in *NF1* mutant flies and mice (2,3). Relatively few data on learning disability based on IQ tests have been reported in molecular or clinical studies on neurofibromatosis.

The *NF1* gene was localized in the region 17q11.2 (4), and its penetrance is virtually 100%. Approximately 50% of the cases represent new mutations, and the expression of the disease is highly variable, both between and within families (1). Because of this variability, population study data are especially valuable to improve genetic counseling for NF1 families and eventually the management of the patients.

With the aim of improving the care given to neurofibromatosis patients, a multidisciplinary neurofibromatosis group called CEPAN (Center of Research and Service in Neurofibromatosis) was created in the Department of Molecular Biology, School of Medicine at São José do Rio Preto, SP, Brazil. The group comprises geneticists, ophthalmologists, dermatologists, neurologists, radiologists, gynecologists, cardiologists, otorhinolaryngologists, pathologists, orthopedists, and psychologists who have established expertise and experience and who have produced publications on NF1 (5-7).

In the present study, we evaluated the clinical features of 55 Brazilian NF1 patients referred to CEPAN by specialists from different clinical areas.

Material and Methods

Fifty-five patients were classified as having NF1 according to the criteria of the National Institutes of Health (NIH) (8). The NIH criteria include at least two of the following findings: 6 or more café-au-lait spots larger than 5 mm in diameter in prepubertal subjects and larger than 15 mm in postpubertal subjects, 2 or more neurofibromas or 1 plexiform neurofibroma, intertriginous freckling, distinctive bone lesions (sphenoid wing dysplasia or pseudoarthrosis), 2 or more Lisch nodules, an optic glioma, or a first-degree relative diagnosed with NF1. Samples from these patients were previously analyzed by molecular biology techniques and the data were recently published (9).

The patients were often referred to CEPAN by dermatologists, but also by general practitioners and specialists from different clinical areas. All subjects were first examined by a general practitioner of the ambulatory care team at the Medical School Hospital of São José do Rio Preto. Each patient's diagnosis was reassessed at CEPAN, and clinical and genetic details were fully documented. The clinical study was performed in accordance with institutional and national review board-approved protocols and written informed consent was obtained from all patients or persons responsible.

A full ophthalmologic evaluation including slit lamp examination for the detection of Lisch nodules was performed. Cognitive functions were assessed using the Wechsler Intelligence Scale for Children or the Wechsler Adult Intelligence Scale tests, and mental retardation was defined as an IQ < 70 (10). The patients' stature was measured using a stadiometer, and the occipitofrontal circumference (OFC) was measured at the largest diameter over the occiput and forehead. Standard population values for stature and OFC by age were obtained from the 1966 Tanner-Whitehouse Table (11). Bone abnormalities were investigated by X-rays of the chest, cranium, spine, and upper and lower limbs (except hands, wrists and ankles). All patients were submitted to an electrocardiogram and electroencephalogram.

Data were analyzed statistically according to the log scale of family income. Family income was used as a socioeconomic status indicator. Using the raw scale this variable did not follow Gauss distribution, which was achieved with the log scale. Person's correlation was used to assess association between IQ values and log family income. To compare mean log family income according

to short stature and learning difficulty we used a two-sample *t*-test with Welch correction for the degrees of freedom. To assess the level of mental retardation an exact 95% confidence interval was calculated.

Results

Fifty-five NF1 patients were assessed during the 24-month period from June 2001 to June 2003. The frequencies of clinical manifestations are summarized in Table 1. The group of patients included 22 males and 33 females. Their mean age was 33 years (range: 2-68 years) at the time of examination and 12 years (range: 1-40 years) at the onset of symptoms, defined as the presence of six or more café-au-lait spots and/or two or more neurofibromas. Thirty-three probands (60%) had an affected first-degree relative (parent or sibling or both).

Six or more café-au-lait spots were found in 98% of NF1 patients. Cutaneous, plexiform and eyelid neurofibromas were present in a total of 96, 40, and 17% of patients, respectively. Axillary freckling was present in 94.5% of patients and inguinal freckling was present in 45%. Lisch nodules were found in 87.5%. The incidences of macrocephaly (51%) and pterygium of the eye (24%) were high in this cohort while optic glioma was observed in one case. Orthopedic abnormalities including kyphosis, kyphoscoliosis and pectus excavatum were found in about 20% of patients, whereas scoliosis was present in 49%. Other complications of NF1 (sinus tachycardia, headache and respiratory problems) were also common.

Of 48 patients whose height was documented, 19 (40%) had short stature (<3 percentile). Cognitive deficits such as mental retardation and learning difficulties were observed in 35 and 76% of patients, respectively. Because, short stature and cognitive deficits may be affected by family income, statistical tests were performed, showing no evidence of correlation between IQ values and log family income ($r = 0.26$; $P = 0.20$) and no evidence of difference between log family income means according to learning difficulty ($P = 0.67$). However, there was evidence of a lower mean log family income

Table 1. Frequencies of the main clinical features of 55 Brazilian patients with neurofibromatosis type 1 (NF1).

Features	Frequency
Sex	
M	40% (22/55)
F	60% (33/55)
Family history of NF1	60% (33/55)
Age at onset of symptoms	
≤5 years	29% (15/52)
>5 years	71% (37/52)
Age at time of examination	
<5 years	5.5% (3/55)
5-18 years	14.5% (8/55)
>18 years	80% (44/55)
≥6 café-au-lait spots	98% (54/55)
≥2 cutaneous neurofibromas	96% (53/55)
Plexiform neurofibroma (s)	40% (22/55)
Freckling	
Axillary	94.5% (52/55)
Inguinal	45% (14/31)
≥2 Lisch nodules	87.5% (42/48)
Short stature (<3rd percentile)	40% (19/48)
Macrocephaly (98th percentile)	51% (23/45)
IQ tests	
Normal intelligence (IQ ≥ 85)	22.5% (9/40)
Borderline intelligence (70 ≤ IQ < 85)	42.5% (17/40)
Mental retardation (IQ < 70)	35% (14/40)
Learning difficulties	76% (38/50)
Other features	
Pterygium (eye)	24% (11/46)
Eyelid neurofibroma	17% (8/48)
Optic glioma	2% (1/47)
Scoliosis	49% (26/53)
Pectus excavatum	23% (12/53)
Kyphoscoliosis	19% (10/53)
Kyphosis	17% (9/53)
Sinus tachycardia	17% (7/42)
Headache	45.5% (25/55)
Respiratory problems	22% (12/55)

The numbers in parentheses indicate the patients with the feature/total of patients analyzed for the feature. When the number is less than the total number of individuals in the study (55 patients) this is due to the fact that the response was coded as "unknown" and these individuals were not included in the table. IQ = intelligence quotient.

in the short stature group (P = 0.20). The estimate of the level of mental retardation was 35% with a 95% confidence from 21 to 52%.

Discussion

We have reported the clinical features of 55 NF1 patients. This report exemplifies the clinical heterogeneity of a population with NF1 and highlights similar and different features between this series of Brazilian patients and other groups of patients.

Many clinical features of the patients were similar to those reported in the literature (Table 2). Indeed, as reported by others (12,13), café-au-lait spots were the most common manifestation, found in 54 of our 55 patients (98%). This feature is usually the first sign in young children and is considered to be the most helpful one leading to diagnosis. Café-au-lait spots are not only found in NF1 patients, and about 20% of individuals in the general population have one or two such skin lesions. Although clinically similar in both groups, the number of café-au-lait spots is significantly higher in NF1 patients (1).

Table 2. Comparison of the frequencies (%) of neurofibromatosis type 1 (NF1) features in eleven studies with the data reported here.

Features	Reference (number of patients)											
	23 (1728)	15 (953)	13 (523)	25 (495)	26 (238)	21 (203)	16 (200)	12 (195)	14 (135)	35 (131)	36 (91)	Present study (55)
CAL	89	100	98	95	NA	78	95.5	98	84	NA	82	98
NF	54	NA	NA	50	NA	NA	49	NA	NA	NA	93	96
Plexiform NF	23	40	15	32	NA	16	25	NA	32	NA	NA	40
Lisch nodules	59	84	63	94	NA	NA	66	93	85	NA	NA	87.5
Freckling												
axillary	NA	NA	84	NA	NA	NA	84	NA	NA	NA	NA	94.5
inguinal	NA	NA	42	NA	NA	NA	52	NA	NA	NA	NA	45
Pseudoarthrosis	2	3	2	3	3	NA	3	NA	4	0	NA	0
Scoliosis	24	25	12	23	29	16	20.5	NA	10	5	≥10	49
Pectus excavatum	NA	NA	NA	NA	NA	NA	7	NA	NA	NA	NA	23
Kyphoscoliosis	NA	NA	NA	NA	NA	NA	NA	13	NA	NA	NA	19
Optic glioma	4	NA	5	10	15	NA	9	10	2	2	0	2
Macrocephaly	NA	NA	NA	38	NA	NA	43	36	45	NA	NA	51
Short stature	NA	NA	NA	18	NA	NA	27	NA	34	NA	NA	40
Learning disabilities	NA	NA	62	NA	30	NA	45	NA	30	NA	NA	76
Mental retardation	NA	NA	NA	NA	NA	NA	NA	14	NA	NA	NA	35
Seizures	6	6	4	5	3	NA	3.5	NA	7	6	3-9	11
Headache	NA	NA	NA	22	NA	NA	9	NA	NA	NA	NA	45.5
Hydrocephalus	4	NA	NA	3	NA	NA	NA	5	NA	NA	NA	0
Psychiatric disorder	NA	NA	NA	NA	NA	NA	2.5	NA	NA	NA	NA	2
Facial asymmetry	8	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	4
Precocious puberty	3.5	NA	NA	5	NA	NA	1.5	NA	NA	NA	NA	0
Delayed puberty	NA	NA	NA	NA	NA	NA	0.5	NA	NA	NA	NA	0
Constipation	NA	NA	NA	NA	NA	NA	2	NA	NA	NA	NA	14.5
Hypertension	4	NA	NA	4	NA	NA	3.5	NA	NA	NA	NA	11
Noonan phenotype	4	NA	NA	9	NA	NA	7	NA	NA	NA	NA	0
Malignancy	5	4	NA	5	NA	5	NA	NA	NA	NA	10	0
CNS tumors	2	NA	9	3	0	NA	2.5	5	0	NA	NA	4
Neurofibrosarcoma	NA	NA	NA	NA	NA	NA	1	0.5	NA	NA	NA	0
Xanthogranulomas	2	2	NA	NA	NA	NA	2	NA	1	NA	NA	0

NA = not analyzed; CAL = café-au-lait spots; NF = neurofibromas; CNS = central nervous system.

Almost all our patients exhibited axillary freckling (94.5%), while 14 of 31 (45%) showed inguinal freckling. The frequency of Lisch nodules (iris hamartomas) was also high (87.5%) in the cases submitted to slit lamp examination. Both freckling and Lisch nodule data were similar to literature reports (13-15).

Some of the NF1 features, such as macrocephaly, short stature and thoracic abnormalities, were present in a significant number of our patients. Macrocephaly and short stature have usually been detected in about 30 to 40% of NF1 patients (14,16). In the present study, 23 of 45 cases (51%) showed an OFC above the 98th percentile, and 40% were at or below the 3rd percentile in height.

Plexiform neurofibroma of the head, early or delayed puberty, optic glioma or hydrocephalus occasionally affect OFC measurements (17). However, among NF1 patients, an increased OFC has frequently no obvious cause and appears to result from overgrowth of the brain. In the present study, no cranial abnormality was found by X-rays. For detection of optic glioma, all patients were investigated by campimetry and suspected cases were also submitted to computed tomography. A single case of optic glioma was detected, and had no effect on the frequency of macrocephaly.

Pseudoarthrosis, early or delayed puberty, optic glioma, scoliosis or vertebral dysplasia may also influence stature (17). Actually, there were no cases of pseudoarthrosis and early or delayed puberty in our cohort and, excluding our patients with scoliosis or vertebral dysplasia (N = 9), short stature was found in only a small number of cases (21%). In these patients, the short stature affected the whole skeleton in a proportionate manner, and no specific cause was apparent.

In the present study, the frequencies of respiratory problems and headache were 22 and 45.5%, respectively. Respiratory problems are uncommon in NF1, but intrapulmonary neurofibromas or scoliosis may cause lung disease. Patients with NF1 may also have headaches as a result of anxiety or depression associated with the disease (18). Only one of our cases had optic glioma and one had ectropion uveae. The incidence of optic gliomas ranges from 1 to 20% in NF1 cases, but only 1-5% develop symptoms (19). Congenital ectropion uveae is occasionally associated with other ocular anomalies and with NF1 (20).

Therefore, the clinical features of the 55 patients were typical of an NF1 phenotype, although an unexpectedly higher incidence of plexiform neurofibromas, mental retardation, learning difficulties, and scoliosis was found. The incidence of plexiform neurofibromas was 40%, similar to the findings of Riccardi (15), but higher than the percentage of 15-32% reported by others (13,14,16,21-25). We also found IQ scores below 70 in 35% of the cases (14 of 40). Fifteen patients refused the IQ tests. Other studies have reported mental retardation frequencies ranging from 3 to 14% (12,15,26-33). Learning difficulties were also reported in 38 of 50 (76%) patients in our study, a value higher than the percentage of 30-62% reported by others (13,14,16,22-24,26-31,33-35). Three children in the preschool age and two illiterate patients were excluded from the analyses because of learning difficulties. In addition, 49% of our patients presented scoliosis, a much higher percentage than the 5 to 29% reported by others (13-16,21,23,25,26,36, 37).

Such differences probably reflect the methods used to assess the data. For example, clinical evaluation may miss some cases of plexiform neurofibromas. Magnetic resonance imaging and histopathological evaluation, as performed by Riccardi (15) and by us, should improve the diagnosis. However, our group of patients is too small to permit a definitive conclusion. With respect to scoliosis, the high incidence found in our sample may be due to evaluation by X-ray and therefore the inclusion of mild

cases, reinforcing the idea that differences in the frequencies of NF1 manifestations are probably caused by the methods of assessing them.

The higher frequency of mental retardation and learning difficulties in our study may reflect the socioeconomic and cultural status of the cohort. Also, this higher frequency may be due to limited psychosocial and environmental stimulation related to the lack of specialized patient and family support in Brazil. However, there was no significant association between IQ values, learning difficulties and family income, a socioeconomic status indicator. Similar results were reported by North et al. (31) and Ferner et al. (32). Also, the frequency of mental retardation in NF1 patients was much higher than expected for the Brazilian population (35 *vs* 5%) according to Tramontina et al. (38).

Descheemaeker et al. (39) observed that the mean full-scale IQ was significantly lower in the NF1 microdeletion group (76.0) compared with the non-microdeletion group (88.5). Our NF1 patients were not screened for this alteration. Thus, it is possible that cases with microdeletion contributed to the higher frequency of mental retardation observed in our cohort.

Several studies have shown that mutations in the NF1 gene cause abnormalities in cell growth and differentiation and lead to a variety of learning disabilities. Neurofibromin has several biochemical functions, such as Ras-guanosine triphosphatase activity, adenylate cyclase modulation, and microtubule binding, all of which could be critical for brain function. A recent study has suggested that the learning disabilities associated with NF1 are caused by excessive Ras activity that leads to increased γ-aminobutyric acid inhibition and to decreased long-term potentiation (40).

Apart from differences in methodology, a precise comparison of different studies is difficult because the frequencies of most NF1 features change with age, and the age distributions of the cohorts probably differ. Moreover, different criteria for the diagnosis and definition of disease manifestations have been used.

Even considering these differences, our study was able to show that mental retardation is common in NF1. In addition to mental retardation, learning difficulties, plexiform neurofibromas, and scoliosis were also common, showing that these features, if accurately investigated, are more common in NF1 than previously thought. This insight may be valuable for genetic counseling and for the management of NF1 patients.

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