











Clinical and epidemiological characterisation of neurofibromatosis type 1: Combined analysis of a reference hospital in Brazil and DataSUS

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Abstract

Neurofibromatosis type 1 (NF1) is a syndrome triggered by mutations in the *NF1* gene, which alter the neurofibromin protein, a negative regulator of the *RAS* oncogenic pathway. Due to underreporting, the scarcity of studies on NF1 in Brazil and its importance in public health. This study aimed to assess the clinical and epidemiological characterisation of NF1 in a Reference Hospital in the country and DataSUS. The study analysed the electronic medical records of patients with NF1 and the DataSUS databases. The medical records showed a greater number of female, white and adult patients. There was a high frequency of clinical features adopted by the NIH consensus for the clinical diagnosis of the disease, such as CALMs, dermal neurofibromas and axillary/inguinal ephelides, bone and ophthalmological changes, in addition malignant and benign neoplasms and neurodevelopmental disorders. On the other hand, the data provided by DataSUS shows a disproportionate concentration of NF1 consultations between the country's regions, with a low level of diagnoses of newborn with NF1 and a NF1 mortality rate of 3.06% in the population. There is therefore a need for new public policies on access to diagnosis, treatment and information about the disease for the Brazilian population.

Keywords: Neurofibromatosis, neurofibroma, neoplasms, nervous system diseases, genetic diseases.

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Introduction

Neurofibromatoses are a class of autosomal dominant diseases, divided into Neurofibromatosis type 1 (NF1; OMIM 162200) (OMIM, 1986), Neurofibromatosis type 2 (NF2) and Schwannomatosis. Of these, NF1 is the most common and has the highest risk of developing into malignant cancer (Pinna *et al.*, 2015; Ly and Blakeley, 2019). It is considered to be a syndrome caused by mutations in the *NF1* gene, which encodes the neurofibromin protein, a negative regulator of the *RAS* oncogenic pathway. Loss of neurofibromin function and activation of the *RAS* results in increased proliferative activity (Eoli *et al.*, 2019; Landry *et al.*, 2021). *NF1* is a tumor suppressor gene, and loss of the wild-type allele is observed in malignancies associated with neurofibromatosis (Carrion *et al.*, 2023). Because of this, individuals with NF1 are more likely to develop malignant or benign tumours in the nervous system, skin or bones (neurofibromas, optic nerve glioma, meningioma and malignant peripheral nerve sheath neoplasia) (Gutmann *et al.*, 2017; Staedtke *et al.*, 2017; Miraglia *et al.*, 2020).

NF1 is an autosomal dominant disease with penetrance is close to 100%, with an incidence of approximately 1 in every 2.500/3.000 individuals, and is one of the most frequent

autosomal diseases in the world population (Uusitalo *et al.*, 2015; Friedman, 2022). Half of the cases of the disease are caused by genetic inheritance factors, but they can also be caused by new mutations (Bayat and Bayat, 2020). The clinical characteristics of NF1 vary greatly between individuals. However, according to the *National Institute of Health (NIH) Consensus Conference*, individuals with NF1 must have two of the seven diagnostic criteria, such as six or more café-au-lait macules (CALMs), axillary or inguinal ephelides, two or more cutaneous or plexiform neurofibromas of different types, two or more lisch nodules (LNS), a specific skeletal lesion, an optic glioma or a first-degree relative affected (NIH, 1988). Café-au-lait macules (CALMs) and ephelides are signs present in both NF1 and Legius Syndrome, so a differential diagnosis must be made (Legius *et al.*, 2021).

The NF1 mutation may also be related to some neurodevelopmental disorders such as cognitive impairment of the speech and motor system, Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), dyslexia, as well as other clinical features such as epilepsy and chronic headache (migraine) (North *et al.*, 1997; Hyman *et al.*, 2005; Pecoraro *et al.*, 2017; Vogel *et al.*, 2017).

Given that NF1 is a syndrome with scarce data in Brazil and of public health importance, the aim of this study was to investigate epidemiological data and the clinical characterisation of patients with NF1 treated at a quaternary reference university hospital in the country. In addition to analysing Brazilian public health databases.

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Subjects and Methods

The retrospective cross-sectional study carried out analysed clinical and epidemiological data on patients with NF1 treated between 2010 and 2020 at a Brazilian quaternary referral hospital (Hospital de Base, n.d.), which treats individuals from more than 102 municipalities and most of the administrative regions of Brazil and Latin America. Data available from the country's Unified Health System (DataSUS) from 2010 to February 2024, which issues general data on diseases and health procedures carried out in the country, was also analysed (Brazil, 2020). Therefore, the analysis of hospital and DataSUS data was evaluated in order to obtain the greatest amount of information on the syndrome analysed.

The hospital's electronic records were searched using the International Statistical Classification of Diseases and Related Health Problems (ICD) "Q85.0" and with "Neurofibromatosis" and the "Neurofibroma" keywords, to find patients diagnosed with NF1. The results of the data from the Reference Hospital showed that 316 patients were obtained, of whom only 187 had their diagnosis confirmed by meeting the clinical criteria and five by molecular tests. Those whose diagnosis was not confirmed because they had insufficient clinical information in their electronic medical records were not included in the analysis of the results. NF1 diagnosis criteria was realized with the NIH (1988) and Legius *et al.* (2021) revised criteria.

The number of cases, family history and clinical data were investigated. Among the information available, age, gender, ethnicity, location, clinical characteristics of the patients, number of deaths and mortality rate were evaluated. The clinical characteristics described were: dermal and plexiform neurofibromas, CALMs, axillary and/or inguinal ephelides, ocular and visual changes (i.e. low visual acuity, strabismus and amblyopia), bone changes (i.e. wing dysplasia of the sphenoid bone), pseudarthrosis, scoliosis, limb dysmetria, LNs, optic nerve glioma, macrocephaly, hydrocephalus, epilepsy, neurological disorders (chronic headache, attention deficit hyperactivity disorder, dyslexia), development of benign and malignant tumours (malignant neoplasm of the peripheral nerve sheath, meningioma, arachnoid cyst, haemangioma, pheochromocytoma and leiomyoma) and precocious puberty.

The data collected on the Department of Informatics of the Unified Health System (DataSUS) platform, was done by following the tabs: "Health Information (TABNET)", "Health Care", "Hospital Production (SIH/SUS)" and "SUS Hospital Procedures – Place of hospitalisation" by region. For the number of treatments, number of deaths and mortality rate, the Contents tab was used, clicking on "AIH approved", "Deaths" and "Mortality rate", following the procedures tab by "0303110082 – neurofibromatosis treatment". Data on births with NF1 was collected using the following tabs: "Vital Statistics", "Live Births – 1994", "Anomaly or Congenital Defect in Live Births – SINASC", "Diagnosis Number", "ICD – Q850" (Brazil, 2012; Brazil, 2022). DataSUS is the country's main public health database, but it has a high level of data scarcity. It is therefore an important tool for the study's data analyses (Aguilar *et al.*, 2022).

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) IBM 23rd version and

GraphPad Prism software version 9. The statistical tests used were Pearson's chi-square test and Fisher's Exact Test. In all analyses, a P-value of less than 0.05 was considered statistically significant.

The study was approved by the Research Ethics Committee of the Faculty of Medicine of São José do Rio Preto under number 3.380.276.

Results

When analyzing the Reference Hospital medical records of the 316 patients examined with suspected NF1, only 192 had a confirmed diagnosis of NF1, giving a prevalence of 60% per case assessed. The medical records revealed a greater number of female (57.8%), white (89.6%), adult (18y-39y) patients (40.6%) and only (9%) had completed higher education, see Table 1.

The NF1 patients in the study presented the clinical features that diagnose the disease according to the NIH (1988) consensus. Dermal neurofibroma, the main feature of NF1, was present in 135 patients. Precocious puberty, a complication associated with the presence of optic nerve glioma, was present in three patients (1.6%). The clinical features and their frequency in the patients can be seen in Table 2.

Of the 192 patients, 7.2% developed malignant neoplasms and 18.7% developed benign neoplasms. Various skeletal and ocular changes were also observed in the individuals, see Table 3.

Nuclear magnetic resonance imaging (MRI) was available in 55 patients and showed hyperintense T2-weighted images in 29 scans, giving an average of 52.7% of the patients examined with a positive result. The most common anatomical locations of these central nervous system lesions were the basal ganglia, cerebellum and trunk.

Neurodevelopmental disorders were present in 35 patients, with an average of 18.2% among NF1 patients. The proportion of women and men with neurodevelopmental disorders was not very different overall, with 17 women and 18 men. However, there were differences in the proportions between the sexes, see Table 4.

Epilepsy was diagnosed in five patients, an average of 2.6%, three of whom had focal epilepsy. Chronic headaches were reported by 24 patients (12.5%), with migraines predominating in 16 (8.4%) and tension headaches in six (3.1%). Macrocephaly was present in five (2.6%) and hydrocephalus in two (1%) patients.

The DataSUS database showed that 1145 people were treated for neurofibromatosis in health centres. The region with the highest number of cases was the Southeast with 465, while the other Brazilian regions were the South with 279, the Northeast with 250, the North with 78 and the Centre-West with 73 (Figure 1). The number of diagnoses of live births with neurofibromatosis was 22 individuals between 2010 and 2022, with an average of two individuals per year.

The number of deaths from neurofibromatosis in Brazil from 2010 to 2024 was 35, with the South and Southeast regions having the highest number of deaths, with 11 and 13, respectively. The country's mortality rate for NF1 is 3.06% of the population.

Table 1 – Incidence and characterisation of the population treated at the hospital with NF1.

Population characteristics	n	%	P-value
Biological sex			<0.0030 **
Female	111	57.8	
Male	81	42.2	
Ethnicity and colour			<0.0001 ****
White	171	89.6	
Brown	12	6.0	
Black	5	2.6	
Data unavailable	4	2.0	
Age			<0.0001 ****
Children and adolescents (4-17y)	55	28.6	
Young people and adults (18-39y)	78	40.6	
Adults and seniors (40-83y)	58	30.2	
Data unavailable	1	0.5	
Level of education			<0.0001 ****
Illiterate	29	15.1	
Primary to secondary education	97	50.5	
University education	18	9.0	
Data unavailable	48	25.0	

*Significant p-value <0,05

Table 2 – Frequency in patients with clinical characteristics adopted in the National Institute of Health Consensus (1988).

Clinical characteristics	n	%
CALM*	178	92.7
Dermal neurofibroma	135	70.3
Axillary and/or inguinal ephelides	127	66.1
Specific bone lesions	120	62.5
Family history	85	44.3
Lisch nodule	56	29.2
Plexiform neurofibroma	44	22.9
Glioma of the optic nerve	8	4.1

*CALM: café-au-lait macules

Table 3 – Malignant and benign neoplasms, bone and eye alterations present in patients with NF1.

Neoplasms and alterations	n	%
Malignant neoplasms	14	7.2
MPNST*	3	1.5
Dermal basal cell carcinoma	3	1.5
Unspecified carcinomas	2	1
Gastrointestinal stromal tumour	1	0.5
Ductal carcinoma	1	0.5
Papillary urothelial carcinoma	1	0.5
Dermal carcinoma unspecified	1	0.5
Dermal squamous cell carcinoma	1	0.5
Papillary thyroid carcinoma	1	0.5
Benign neoplasms	36	18.75
Central nervous system cancer	29	15.1
Pheochromocytoma	2	1
Hemangioma	2	1
Meningioma	1	0.5

Table 3 – Cont.

Neoplasms and alterations	n	%
Arachnoid cyst	1	0.5
Thyroglossal duct cysts	1	0.5
Ophthalmic alterations	28	14.5
Low visual acuity	22	11.45
Strabismus	5	2.6
Amblyopia	1	0.5
Skeletal alterations	120	62.5
Scoliosis	59	30.7
Pectus excavatum	16	8.3
Hyperkyphosis	15	7.8
Hyperlordosis	6	3.1
Lower limb dysmetria	5	2.6
Flat feet	4	2.1
Genu Valgum	4	2.1
Congenital clubfoot	3	1.5
Pseudoarthrosis	3	1.5
Sphenoid wing dysplasia	3	1.5
Pectus Carinatum	1	0.5
Genu varus	1	0.5

*MPNST: Malignant peripheral nerve sheath tumour

Table 4 – Frequency of neurodevelopmental disorders in the sexes of patients with NF1.

Neurodevelopmental disorders	Male			Female			P-value
	n	P	%	n	P	%	
Cognitive impairment	7		8.6	12		10.8	0.8074
Speech impairment	7		8.6	6		5.4	0.3981
Motor impairment	5	81	6.1	3	111	2.7	0.2854
ADHD	7		8.6	4		3.6	0.2077
ASD	4		4.9	0		0	0.0303*
Dyslexia	2		2.4	0		0	0.1767

Note: P, population; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder. *Significant p-value <0,05 (Some patients had more than one associated disorder)

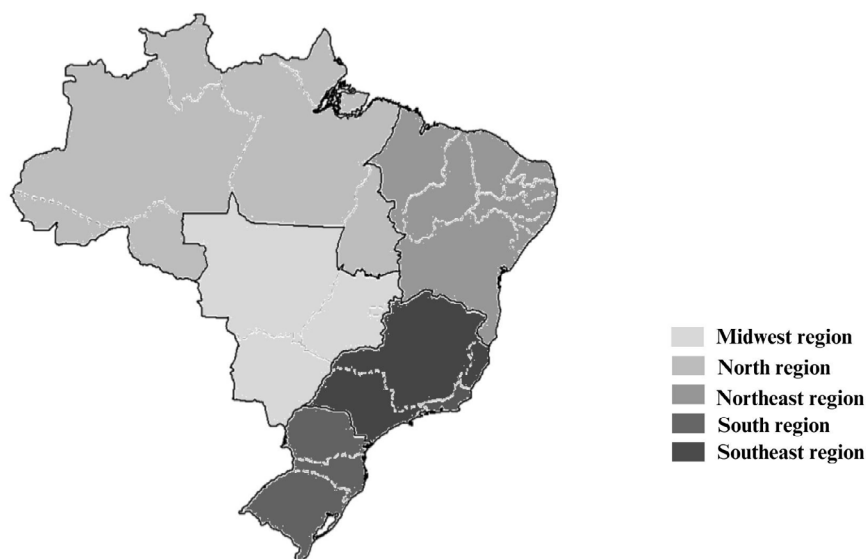


Figure 1 – Number of treatments for neurofibromatosis in Brazilian regions from 2010 to 2024, according to DataSUS. The registration of NF1 cases number varies between light grey (n=73) to black colour (n=465).

Discussion

The difficulty in diagnosing patients and the lack of knowledge among health professionals about neurofibromatosis type I (NF1) resulted in 40% of undiagnosed cases. It is therefore necessary to broaden the understanding of these professionals, and molecular tests, which are not available in Brazilian public health, could help with the genotype-phenotype relationship and patient follow-up. This deficit reduces the depth and attention of the clinical investigation of the disease (Iriart *et al.*, 2019).

Studies show that NF1 has the same incidence between genders and ethnicities (Friedman, 1999; Ly and Blakeley, 2019). However, the present study observed a higher incidence of NF1 in females and in white people. In agreement with our study, Landry *et al.* (2021) reported that 52.3% of patients were female. These results are related to the specificity of the population studied, since men seek health services less than women and the country's dark-skinned population is the most affected by poverty, lack of information and access to health services (Levorato *et al.*, 2014; Silva *et al.*, 2020). These factors are intrinsic to the results on gender, ethnicity and the incidence of NF1 in the population studied.

The Brazilian regions with the highest frequency of care for NF1 were the South and Southeast, related to the concentration of public health care in these regions (Oliveira *et al.*, 2019). On the other hand, the North and Centre-West regions had a lower number of patients treated, as they are regions with geographical barriers, limited access to healthcare and a lack of public policies (Oliveira *et al.*, 2019).

The results showed that 35 people in the country died from NF1, with a mortality rate of 3.06%. According to the literature, patients with NF1 have their life expectancy reduced by up to 15 years compared to the general population (Rasmussen *et al.*, 2001). Malignant tumours and vascular diseases are the main factors associated with death in these patients, with a higher frequency in patients under the age of 40 (Landry *et al.*, 2021).

The number of children born with NF1 in Brazil between 2010 and 2022 was 22 individuals. This low number is justified because children with NF1 show few characteristics of the disease during the early stages of development and only around 50% have familial history. NF1 is a progressive disease and presents greater characteristics in adulthood. However, CALMs and other clinical features of the disease can occur during the early stages of development (Rasmussen *et al.*, 2001; Tamura, 2021).

In this study, adults were the most commonly diagnosed, as symptoms appear and progress gradually over time (Rasmussen *et al.*, 2001; Tamura, 2021). Consistent with our findings, one study showed that the median age at which diagnosis was sought was 19 years (Landry *et al.*, 2021). Late diagnosis is also related to the low number of people seeking treatment in the early stages, due to a lack of information about the disease and the low education level of the population (Rasmussen *et al.*, 2001; Wang *et al.*, 2010). NF1 can usually be diagnosed by assessing the individual's family history and by physical examination (Hirbe and Gutmann, 2014; Gutmann *et al.*, 2017). Of the patients in the study, 44.3% had a history of NF1 in other family members.

The presence of CALMs is the first and most common feature to be assessed (Ben-Shachar *et al.*, 2017; Lalor *et al.*, 2020). In our study, 92.7% of patients had CALMs, which is a predictive symptom for the diagnosis of NF1 (Lalor *et al.*, 2020; Kehrer-Sawatzki and Cooper, 2022). Another common feature in patients with NF1 is axillary or inguinal freckling, which was present in more than 65% of individuals in our study. The results are in agreement with a study from 2020, which showed that axillary or inguinal freckling is present in 90% of individuals with NF1 (Miraglia *et al.*, 2020).

Diagnostic ocular manifestations may occur in early childhood, such as optic nerve glioma (OPG), or in late childhood and adolescence, such as LNs (Senthilkumar and Tripathy, 2023). OPGs tend to develop slowly, are more indolent in NF1 patients, and are generally asymptomatic (Bajenaru *et al.*, 2005; Ferner *et al.*, 2007). OPG had a low frequency (4.1%) in the present study, as only patient-reported complaints were included in the medical records, and most of these lesions are indolent. For LNs, 29.2% of patients had this characteristic. However, we observed a lower prevalence of LNs in the study population compared to data in the literature. LNs are considered the most typical clinical feature of the syndrome and are present in 95% of patients with NF1 (Iheanacho *et al.*, 2022).

Neurofibromas are classified as benign tumours of the peripheral nerve sheath. They can cause local itching, pain, motor difficulties and sensory problems (Rad and Tee, 2016; Flores *et al.*, 2022). In this study, 93.2% of patients had neurofibromas. A high frequency was also observed by Miraglia *et al.* (2020), in which 78.1% of patients had some type of neurofibroma (Miraglia *et al.*, 2020). In addition, individuals with NF1 have a high risk of developing neoplasms compared to the general population, with an incidence of 10% of cases (Eoli *et al.*, 2019; Landry *et al.*, 2021). In our study, 26.04% of NF1 patients developed neoplasms other than neurofibromas. Among the most common neoplasms in our study, MPNST, pheochromocytoma and central nervous system cancer were also the most frequent in a study carried out in 2016 (Landry *et al.*, 2021).

Alterations to bones were present in 62.5% of patients. These skeletal anomalies occur due to the absence of two copies of the NF1 gene in osteoclasts and osteoblasts, cells essential for bone resorption and formation, respectively (Hirbe and Gutmann, 2014). We found that 30.7% of the patients had scoliosis or more than one skeletal anomaly. According to the literature, the most common bone lesions are scoliosis, kyphosis and spinal deformity, with a range of prevalence of 8% to 60% (Larson *et al.*, 2018).

In a study carried out on rats, high *RAS* activity was correlated with increased GABA activity and changes in dopaminergic activity, which are associated with behavioural disorders such as attention deficit hyperactivity disorder, autism, dyslexia and cognitive difficulties (Gutmann *et al.*, 2017; Bayat and Bayat, 2020; Kaczorowski *et al.*, 2020). In the present study, 35 patients were found to have neurodevelopmental disorders, with males having the highest frequency. According to the literature, male patients are more prone to neurodevelopmental disorders (Jorge, 1995). Other neurological disorders, such as epilepsy and migraine,

were also found in this study. Such disorders are frequent in individuals with NF1, such as migraine, which can be present in up to 33% of the cases (Pecoraro *et al.*, 2017; Vogel *et al.*, 2017; Miller *et al.*, 2019).

Conclusions

The study population with NF1 shows a high frequency of diagnostic features adopted by the NIH consensus, such as CALMs, axillary/inguinal ephelides, dermal neurofibromas and specific bone lesions, ophthalmological alterations, in addition to malignant and benign neoplasms and neurological disorders. The DataSUS database shows disparity in NF1 care in the North and Centre-West regions, as well as the low number of live births with the syndrome in the country. Therefore, due to the scarcity of data in public databases, the limitation of molecular tests and knowledge of health professionals in rare diseases, there is a need for new public policies for access to diagnoses, treatments and information about the disease for the Brazilian population.

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Conflict of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicial to the impartiality of the reported research.

Author Contributions

MGSL analysed the data and wrote the manuscript; PJM and JOM reviewed the literature, created the figures and tables, analysed the data, wrote the manuscript and formatted the manuscript for submission; MCAN analysed the data and wrote the manuscript; APSV collected the data; MMUCN revised, wrote and carried out the statistical analyses; ECP and ENMGB supervised and revised the manuscript. All authors read and approved the final version.

References

- Aguiar TS, Fonseca MC, Santos MC dos, Nicoletti GP, Alcoforado DSG, Santos SCD dos, Pontes M de L, Soares TFR, Marcos GC, Teixeira SCM *et al.* (2022) Epidemiological profile of meningitis in Brazil, based on data from DataSUS in the years 2020 and 2021. *RSD* 11:1-20
- Bajenaru ML, Garbow JR, Perry A, Hernandez MR and Gutmann DH (2005) Natural history of neurofibromatosis 1-associated optic nerve glioma in mice. *Ann Neurol* 57:119-127.
- Bayat M and Bayat A (2020) Neurological manifestations of neurofibromatosis: A review. *Neurol Sci* 41:2685-2690.
- Ben-Shachar S, Dubov T, Toledano-Alhadeff H, Mashiah J, Sprecher E, Constantini S, Leshno M and Messiaen LM (2017) Predicting neurofibromatosis type 1 risk among children with isolated café-au-lait macules. *J Am Acad Dermatol* 76:1077-1083.
- Carrion AW, Shah AC and Kotch C (2023) Neurofibromatosis type 1-associated gliomas and other tumors: A new pathway forward? *J Pediatr Hematol Oncol Nurs* 8:129-135.
- Eoli M, Saletti V and Finocchiaro G (2019) Neurological malignancies in neurofibromatosis type 1. *Curr Opin Oncol* 31:554-561.
- Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, Evans DG, Upadhyaya M, Towers R, Gleeson M, Steiger C *et al.* (2007) Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet* 44:81-88.
- Flores Pimentel M, Heath A, Wan MJ, Hussein R, Leahy KE, MacDonald H, Tavares E, VandenHoven C, MacNeill K, Kannu P *et al.* (2022) Prevalence of choroidal abnormalities and lisch nodules in children meeting clinical and molecular diagnosis of neurofibromatosis type 1. *Transl Vis Sci Technol* 11:10.
- Friedman JM (1999) Epidemiology of neurofibromatosis type 1. *Am J Med Genet* 89:1-6.
- Friedman JM (2022) Neurofibromatosis 1. 1998 Oct 2 [Updated 2022 Apr 21]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE and Amemiya A (ed) *GeneReviews®*. University of Washington, Seattle. pp. 1993-2025.
- Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL and Johnson KJ (2017) Neurofibromatosis type 1. *Nat Rev Dis Primers* 3:17004.
- Hirbe AC and Gutmann DH (2014) Neurofibromatosis type 1: A multidisciplinary approach to care. *Lancet Neurol* 13:834-843.
- Hyman SL, Shores A and North KN (2005) The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology* 65:1037-1044.
- Iheanacho I, Yoo HK, Yang X, Dodman S, Hughes R and Amin S (2022) Epidemiological and clinical burden associated with plexiform neurofibromas in pediatric neurofibromatosis type-1 (NF-1): A systematic literature review. *Neurol Sci* 43:1281-1293.
- Iriart JAB, Nucci MF, Muniz TP, Viana GB, Aureliano W de A and Gibbon S (2019). Da busca pelo diagnóstico às incertezas do tratamento: desafios do cuidado para as doenças genéticas raras no Brasil. *Ciênc Saúde Coletiva* 24:3637-3650.
- Jorge, MR (1995) *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Artmed, Porto Alegre.
- Kaczorowski JA, Smith TF, Shrewsbury AM, Thomas LR, Knopik VS and Acosta MT (2020) Neurofibromatosis type 1 implicates ras pathways in the genetic architecture of neurodevelopmental disorders. *Behav Genet* 50:191-202.
- Kehrer-Sawatzki H and Cooper DN (2022) Challenges in the diagnosis of neurofibromatosis type 1 (NF1) in young children facilitated by means of revised diagnostic criteria including genetic testing for pathogenic NF1 gene variants. *Hum Genet* 141:177-191.
- Lalor L, Davies OMT, Basel D and Siegel DH (2020) Café au lait spots: When and how to pursue their genetic origins. *Clin Dermatol* 38:421-431.
- Landry JP, Schertz KL, Chiang YJ, Bhalla AD, Yi M, Keung EZ, Scally CP, Feig BW, Hunt KK, Roland CL *et al.* (2021) Comparison of cancer prevalence in patients with neurofibromatosis type 1 at an academic cancer center vs in the general population from 1985 to 2020. *JAMA Netw Open* 4:e210945.
- Larson AN, Ledonio CGT, Brearley AM, Sucato DJ, Carreon LY, Crawford AH, Stevenson DA, Vitale MG, Moertel CL and Polly DW Jr (2018) Predictive value and interrater reliability of radiographic factors in neurofibromatosis patients with dystrophic scoliosis. *Spine Deform* 6:560-567.
- Legius E, Messiaen L, Wolkenstein P, Pancha P, Avery RA, Berman Y, Blakeley J, Babovic-Vuksanovic D, Cunha KS, Ferner R *et al.* (2021) International consensus group on neurofibromatosis diagnostic Criteria (I-NF-DC); Huson SM, Evans DG, Plotkin SR. Revised diagnostic criteria for neurofibromatosis type 1 and legius syndrome: An international consensus recommendation. *Genet Med* 23:1506-1513.
- Levorato CD, Mello LM de, Silva AS da and Nunes AA (2014) Factors associated with the demand for health services from a gender-relational perspective. *Ciênc Saúde Coletiva* 19:1263-1274.

- Ly KI and Blakeley JO (2019) The diagnosis and management of neurofibromatosis type 1. *Med Clin North Am* 103:1035-1054.
- Miller DT, Freedenberg D, Schorry E, Ullrich NJ, Viskochil D and Korf BR (2019) Council on genetics and american college of medical genetics and genomics. Health supervision for children with neurofibromatosis type 1. *Pediatrics* 143:e20190660.
- Miraglia E, Moliterni E, Iacovino C, Roberti V, Laghi A, Moramarco A and Giustini S (2020) Cutaneous manifestations in neurofibromatosis type 1. *Clin Ter* 171:e371-e377.
- National Institutes of Health Consensus Development Conference (NIH) (1988) Neurofibromatosis. Conference Statement. *Arch Neurol* 45:575-8.
- North KN, Riccardi V, Samango-Sprouse C, Ferner R, Moore B, Legius E, Ratner N and Denckla MB (1997) Cognitive function and academic performance in neurofibromatosis. 1: Consensus statement from the *NF1* Cognitive Disorders Task Force. *Neurology* 48:1121-1127.
- Oliveira RAD, Duarte CMR, Pavão ALB and Viacava F (2019) Barreiras de acesso aos serviços em cinco regiões de saúde do Brasil: percepção de gestores e profissionais do Sistema Único de Saúde. *Cad Saúde Pública* 35:e00120718.
- Pinna V, Lanari V, Daniele P, Consoli F, Agolini E, Margiotti K, Bottillo I, Torrente I, Bruselles A, Fusilli C *et al.* (2015) p.Arg1809Cys substitution in neurofibromin is associated with a distinctive *NF1* phenotype without neurofibromas. *Eur J Hum Genet* 23:1068-1071.
- Pecoraro A, Arehart E, Gallentine W, Radtke R, Smith E, Pizoli C, Kansagra S, Abdelnour E, McLendon R and Mikati MA (2017) Epilepsy in neurofibromatosis type 1. *Epilepsy Behav* 73:137-141.
- Rad E and Tee AR (2016) Neurofibromatosis type 1: Fundamental insights into cell signalling and cancer. *Semin Cell Dev Biol* 52:39-46.
- Rasmussen SA, Yang Q and Friedman JM (2001) Mortality in neurofibromatosis 1: An analysis using U.S. death certificates. *Am J Hum Genet* 68:1110-1118.
- Senthilkumar VA and Tripathy K (2023) Lisch Nodules. StatPearls Publishing LLC, Florida.
- Silva NN, Favacho VBC, Boska GA, Andrade EC, Merces NP and Oliveira MAF (2020) Access of the black population to health services: Integrative review. *Rev Bras Enferm* 73:e20180834.
- Staedtke V, Bai RY and Blakeley JO (2017) Cancer of the peripheral nerve in neurofibromatosis type 1. *Neurotherapeutics* 14:298-306.
- Tamura R (2021) Current understanding of neurofibromatosis type 1, 2, and schwannomatosis. *Int J Mol Sci* 22:5850.
- Uusitalo E, Leppävirta J, Koffert A, Suominen S, Vahtera J, Vahlberg T, Pöyhönen M, Peltonen J and Peltonen S (2015) Incidence and mortality of neurofibromatosis: A total population study in Finland. *J Invest Dermatol* 135:904-906.
- Vogel AC, Gutmann DH and Morris SM (2017) Neurodevelopmental disorders in children with neurofibromatosis type 1. *Dev Med Child Neurol* 59:1112-1116.
- Wang F, Luo L, McLafferty S (2010). Healthcare access, socioeconomic factors and late-stage cancer diagnosis: An exploratory spatial analysis and public policy implication. *Int J Public* 5:237-258.

Internet Resources

- Brazil, Ministry of Health (2012) Information technology at the service of the SUS (DATASUS), <https://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/qiuf.def> (accessed 4 January 2024).
- Brazil, Ministry of Health (2020) DataSUS (TabNet), <https://datasus.saude.gov.br/informacoes-de-saude-tabnet/> (accessed 15 November 2023).
- Brazil, Ministry of Health (2022) Congenital anomaly or defect in live birth (SINASC-DATASUS), <https://tabnet.datasus.gov.br/cgi/deftohtm.exe?SINASC/anomalias/anomabr.def> (accessed 15 November 2023).
- Hospital de Base (n.d.) <https://www.hospitaldebase.com.br/abrangencia> (accessed 10 January 2024).
- Online Catalog of Human Genes and Genetic Disorders (OMIM) (1986) <https://www.omim.org/entry/162200?search=Nf1&highlight=nf> (accessed 15 November 2023)

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