Phenotypic and Genotypic Variability in Niemann-Pick Type C: A Brazilian Case Series

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Abstract

Niemann-Pick disease type C (NPC) disease is a lysosomal storage disorder caused by alterations in the trafficking of unesterified cholesterol due to mutations in the NPC1 and NPC2 genes. Its manifestations can be visceral, neurological, and psychiatric. This study conducts a retrospective review to assess the clinical, laboratory, molecular, and imaging features of a cohort of Brazilian patients with NPC. Eleven cases were included, 6 females and 5 males, aged between 3 and 32 years. Three cases corresponded to the early infantile form, three to the late infantile form, four to the juvenile, and one to the adult form. The most frequent symptoms were splenomegaly (10/11), hepatomegaly (8/11), vertical supranuclear gaze palsy (11/11), ataxia (10/11), dysarthria (10/11), dysphagia (10/11), spasticity (7/11), epilepsy (7/11), dystonia (7/11), cognitive impairment (8/11), and school delay (8/11). All patients exhibited non-specific abnormalities in brain imaging studies. Biomarker-specific tests were positive in 9 out of 11 cases. The Filipin test was "classic" in 6 cases and "variant" in 5. Mutations in NPC1 were identified in all patients, with the most prevalent variant being p.Ala1035Val (8/11). This case series highlights the p.Ala1035Val mutation in NPC1 correlates with the "classic" profile of Filipin staining.

Keywords

Adults, Genes, Youth, Children, Niemann-Pick C, Filipin Staining.

Introduction

Niemann-Pick Type C (NPC) is a rare hereditary lysosomal storage disorder caused by autosomal recessive mutations in the NPC1 and NPC2 genes. The estimated incidence of NPC is 1 in 100,000 to 120,000 live births in the United States and Europe [1,2], but this figure is likely an underestimate, with more diagnoses occurring when massive screening techniques are employed [3].

NPC can manifest from infancy to adulthood. Patients may be asymptomatic in early life or present with a visceral form at birth. Neurological, psychiatric, and visceral manifestations may emerge shortly after or years later, developing gradually and progressively. The clinical manifestations of NPC1 and NPC2 are similar, as the respective genes participate in the same metabolic process, with their proteins playing auxiliary roles in a common pathway for lipid transport [4,5]. The variable phenotypic expression of the disease is secondary to the accumulation of unesterified cholesterol and glycosphingolipids (GSLs) in tissues and organs, particularly the brain [6].

Hepatic, splenic, and pulmonary involvement is present in more than 85% of patients and precedes the development of neurological symptoms [1,5]. Neurodegeneration associated with behavioral disorders and cognitive impairment generally begins with symptoms such as cerebellar ataxia, supranuclear gaze palsy, dystonia, dysarthria, cataplexy, and extrapyramidal signs. The progression and symptoms of the disease vary according to the age of onset of neurological manifestations, resulting in five different clinical forms. These forms include neonatal (onset before 3 months), early infantile (from 3 months to 2 years), late

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infantile (from 2 to 6 years), juvenile (from 6 to 15 years), and adolescent/adult (over 15 years) [7,8].

Patients suspected of having NPC require ophthalmological, auditory, neurological, and psychiatric evaluations, in addition to biomarker testing. In cases of high clinical suspicion, the measurement of oxysterols serves as the first-line screening test, alongside the assessment of lysosphingolipids and bile acids [5,6]. However, the diagnosis is confirmed through genetic studies. Biallelic pathogenic variants in NPC1 gene account for approximately 95% of NPC cases, while NPC2 mutations account for about 5% [9]. The diagnosis is confirmed when two alleles with mutations in the NPC1 or NPC2 gene are identified. In situations where the diagnosis remains uncertain, a skin biopsy with fibroblast cell culture and Filipin staining can be used as an additional tool for disease confirmation [10,11].

At present, no curative therapy is available for NPC. Treatment focuses on symptom management and is carried out by a multidisciplinary team. Currently, miglustat, (Zavesca™; Actelion Pharmaceuticals Ltd), inhibitor of the synthesis of GSLs is the first and only targeted therapy to be approved for the treatment of NPC. [12,13]. Other treatments are undergoing investigation.

Despite advancements in screening and diagnostic methods, many patients remain undiagnosed or misdiagnosed, delaying timely therapeutic interventions. The progressive and multisystemic nature of NPC reinforces the necessity for ongoing research to optimize the accessibility and accuracy of diagnostic tools and to advance the understanding of genotype-phenotype correlations.

The aim of this study is to describe the clinical and genotypic characteristics of patients with NPC who were followed up at the Hospital das Clínicas de Ribeirão Preto, University of São Paulo (HC-FMRP/USP), Brazil, between 2000 to 2014.

Methods

This is a retrospective, cross-sectional, descriptive study based on a review of medical records of patients treated at the Neurogenetics Outpatient Clinic of HC-FMRP/USP. All records with diagnoses of other sphingolipidoses (ICD E75.2), unspecified sphingolipidoses (E75.3), and unspecified lipid storage disorders (ICD E75.6) between 2000 and 2014 were reviewed. Only those patients with NPC who had a confirmatory genetic test were included in the study. Information was collected through a form that included sociodemographic characteristics (age, sex, race, place of origin), clinical data (history of symptoms and clinical signs, age at diagnosis, treatment with substrate reduction therapy, clinical form, presence of jaundice, visceromegaly, neurological signs), and results of relevant complementary tests. The severity of the disease was assessed using the NPC-specific disability scale, which involves summing scores across four main functional areas: ambulation, manipulation, language, and swallowing [14]. The scoring ranges from 4 (normal function) to 18 (severe disability).

All patients underwent skin biopsies for Filipin staining, and blood sampling for the measurement of specific lysosphingolipids and oxysterols, respectively. The skin biopsy samples were then sent for fibroblast culturing to the NPC Brazil Network, associated with the Medical Genetics Service at the Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul. The staining pattern of the samples was classified into three categories: normal Filipin test (clear negative fluorescence), atypical or "variant" (moderate fluorescence), and typical or "classic" (high fluorescence) [15]. Specific plasma biomarkers, Lysosphingomyelin-509 (Lyso-SM-509) and/or Cholestane-3β,5α,6β-triol (C-triol), were measured at Universitätsklinikum Münster in Münster, Germany.

Genetic testing was carried out in collaboration with the University of Rostock, Albrechgt-Kossel-Institute for Neurogeneration (AKos). All coding exons of the NPC1 and NPC2 genes were sequenced by PCR amplification of DNA. The variants found were classified according to the recommendations of the American College of Medical Genetics.

Data were analyzed using descriptive statistics calculated with spreadsheet software. This research was approved by the Research Ethics Committee of HC-FMRP-USP, under CAAE number: 39788214.3.0000.5440.

Results

A total of 114 medical records were reviewed, and 11 patients with a confirmed diagnosis of NPC by genetic testing were selected. Of these patients, 6 were female (two siblings) and 5 male, with an age range of 3 to 32 years. The majority (9 out of 11) were of white race and originated from the state of São Paulo, Brazil.

Clinical Characteristics

According to the clinical classification of NPC [7], among the 11 selected cases, 3 corresponded to the early infantile form, 3 to the late infantile form, 4 to the juvenile form, and 1 to the adult form. The progression of systemic, neurological, and psychiatric symptoms, biomarker positivity, and the disability scale in these patients are detailed in Table 1.

Regarding systemic symptoms, prolonged jaundice was present in all patients with the early infantile clinical form and in 2 patients with the juvenile form. In addition, hepatomegaly was present in 8 of the 11 patients evaluated, while splenomegaly was identified in 10 of the 11 cases. In patients with the early infantile clinical form, splenomegaly was observed from birth.

Neurological symptoms were present in all patients in the study, independently of the clinical form of NPC. Vertical gaze palsy was the most common symptom, present in all cases. Other symptoms such as ataxia/falls, dysphagia, and dysarthria were observed in 10 of the 11 patients. In addition, epilepsy and spasticity were reported in 7 and 9 patients, respectively. Myoclonus, dystonia, and muscle weakness were identified in

a smaller proportion. Gelastic cataplexy [16], was reported in only one patient with the early infantile clinical presentation.

Concerning psychiatric symptoms, 2 patients with the juvenile form had psychotic episodes, while behavioral disorders were observed in 6 of the 11 cases. Additionally, cognitive decline and school delay were reported in 8 of the 11 patients.

Blood samples from all cases were collected to measure specific biomarkers for NPC [5]. The oxysterol cholestane-3β,5α,6β-triol (C-triol), also known as cholestantriol, was measured in five patients, all of whom showed elevated concentrations. Similarly, lysosphingomyelin-509 (Lyso-SM-509) levels were elevated in six of the eight patients tested.

Disease follow-up after diagnosis ranged from 2 to 9 years with a mean time of 5 years. NPC-specific disability scale [14] scores ranged from 4 to 8 (mean: 7.4) at disease diagnosis and from 7 to 18 (mean: 12.2) at final follow-up. One patient with the early infantile clinical form (Case 2) died at the age of 7 due to respiratory complications.

Medical records revealed that all patients received substrate reduction therapy with miglustat; however, systematically collected information about side effects and disease progression was not available.

Laboratory and Imaging Characteristics

Analysis of cranial magnetic resonance imaging (MRI) images (Table 1 and Figure 1) revealed three patterns of alteration, each occurring with the same frequency: cerebral atrophy (63%), cerebellar atrophy (63%), and demyelination (63%). Six patients exhibited two alterations, three showed one alteration, and two presented with all three alterations.

The results of the molecular study and Filipin test are presented in Table 2. Filipin staining indicated a "classic" result in 6 patients: 2 in the early infantile form, 3 in the late infantile form, and 1 in the juvenile form. In the other 5 patients, the test was classified as "variant." Mutations in the NPC1 gene were identified in all patients. The c.3104C>T mutation was the most prevalent, present in 8 of the 11 patients, 4 in homozygous state and 4 in compound heterozygosity. Additionally, other mutations in homozygous state were identified in the remaining 3 patients: c.3493G>A, c.3019C>G, and c.3548G>A.

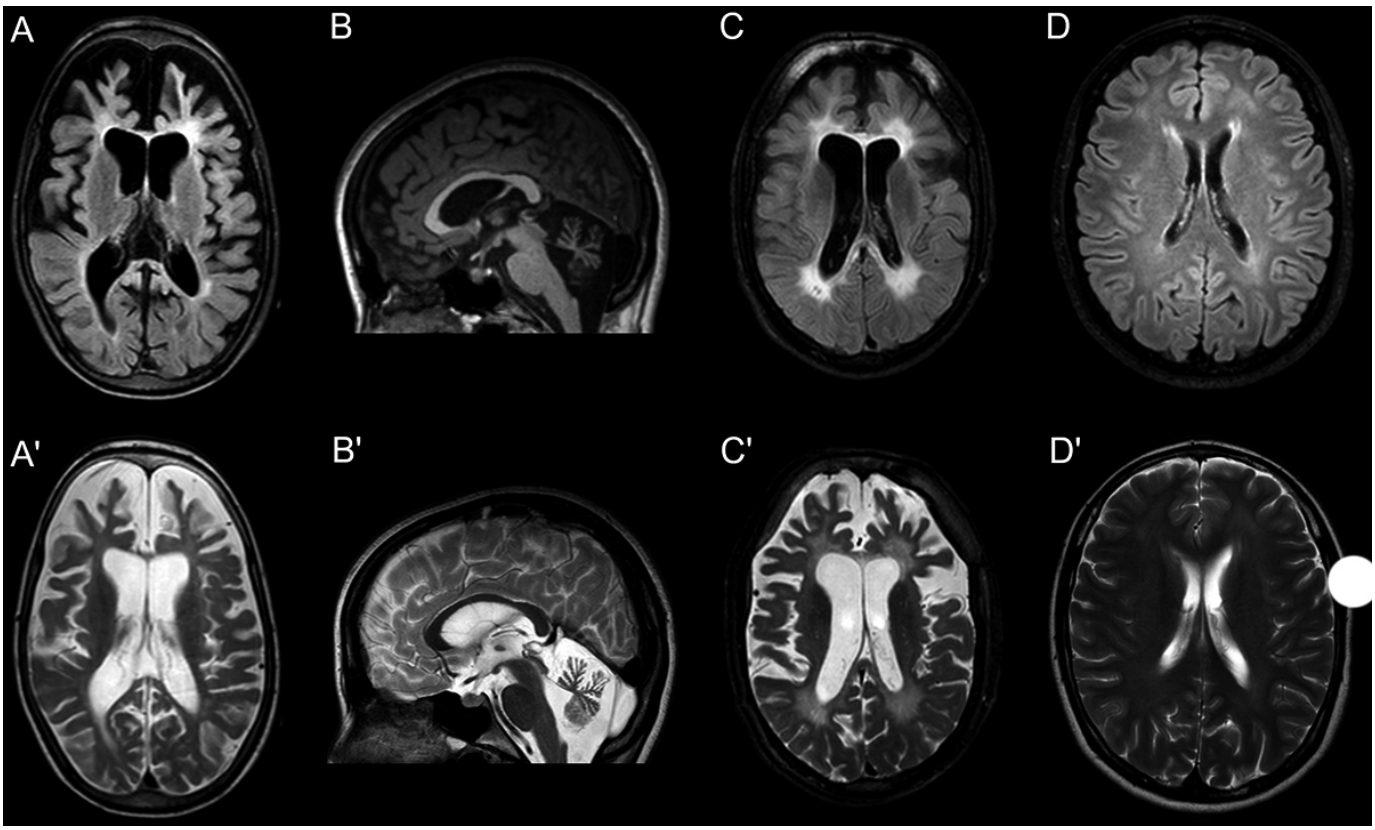

Figure 1. Axial (A, C, D) and sagittal (B) MRI images (FLAIR, T1-weighted, [A-D], and T2-weighted, [A'-D']) illustrating cases of the early infantile (A-A'), late infantile (B-B'), juvenile (C-C'), and adult (D-D') forms of Niemann-Pick Type C. Panels A and C demonstrate pronounced volumetric cerebral atrophy and diffuse demyelination (cases 3 and 9). Panel B highlights accentuated cerebellar atrophy (case 4). Panel D shows mild demyelination (case 11).

Table 1. Sociodemographic and clinical characteristics of patients with Niemann-Pick Type C.

Variable		Total	Early infantile form			Late infantile form				Juvenile form			Adult form
Patient identification		11	1	2 †	3	4*	5*	6	7	8	9	10	11
Sex (Male: Female)		5:6	F	F	M	F	F	M	M	F	M	M	F
Race (White: Mixed)		9:2	Mixed	White	White	White	White	White	White	White	White	Mixed	White
Age (years) at last exam		3-32	3	7	12	20	16	17	28	26	23	19	32
Tests: Biomarker screening for NPC		9/11	↑ Lyso-509	↑ Lyso-509	↑ C-triol	↑ Lyso-509 ↑ C-triol	↑ C-triol	↑ C-triol	↔ Lyso-509	↑ Lyso-509	↑ Lyso-509 ↑ C-triol	↑ Lyso-509	↔ Lyso-509
Clinical Symptom Progression (years)	Prolonged jaundice	5/11	+	+	+				+	+			
	Splenomegaly	10/11	+	+	+	+	+	+	+	+	+	+	
	Hepatomegaly	8/11	+	+	+		+	+	+	+	+		
	Age at first neurological signs	1-16	1	1	3	6	6	6	15	15	7	11	16
	Ataxia/falls	10/11	2		4	6	12	6	17	18	9	12	16
	Vertical Gaze Palsy	11/11	3	3	4	12	12	12	23	18	10	17	24
	Dysarthria	10/11	2		3	6	13	8	22	20	10	13	24
	Dysphagia	10/11	3		4	9	14	15	21	20	14	13	24
	Spasticity	9/11	3	4	4			13	23	24	16	13	30
	Epilepsy	7/11		1	4		16	6	16		13	17	
	Dystonia	7/11	2			15		8	23	23	19	17	18
	Muscle weakness	5/11		4	4				25		16		30
	Myoclonus	3/11			6			8			22		
	Gelastic cataplexy	1/11		4									
	Cognitive decline/ dementia	8/11	3		5		6	14	16	20	12	17	
	Lack of achievement in school	8/11			+	+	+	+	+	+	+	+	
	Behavioral disorders	6/11			3	20	15	14	17	16			
	Psychotic symptoms	2/11							17	20			
Treatment: Age at onset of Miglustat		2-31	2	2	8	16	13	13	24	22	19	18	31
Years of follow-up (mean)		5	2	7	9	5	6	4	5	4	4	5	4
Disability score at diagnosis (mean)		7,4	4	6	4	8	7	8	7	7	13	9	8
Disability score at last follow-up (mean)		12,2	10	9	16	8	7	15	16	7	18	18	10
Brain MRI	Demyelination	7/11		+	+			+	+	+	+		+
	Cerebral atrophy	7/11	+		+	+		+	+		+		+
	Cerebellar atrophy	7/11	+		+	+	+	+		+		+	

* Siblings; † Died; Lyso-509: Lysosphingomyelin-509 (Lyso-SM-509); C-triol: cholestane-3β,5α,6β-triol / cholestantriol, ↑ Elevated concentration, ↔ Normal concentration

Table 2. Molecular characteristics and Filipin staining in patients with Niemann-Pick Type C.

Clinical form	Case	Gen	Variant	Nucleotide	Estado	Classification	Filipin
Early infantile	1	NPC1	c.3104C>T	p.Ala1035Val	Homozygous	Pathogenic	Classic
	2	NPC1	c.3104C>T	p.Ala1035Val	Homozygous	Pathogenic	Classic
	3	NPC1	c.3104C>T	p.Ala1035Val	Compound heterozygous	Pathogenic	Variant
			c.3182T>C	p.Ile1061Thr		Pathogenic	
Late infantile	4**	NPC1	c.3104C>T	p.Ala1035Val	Homozygous	Pathogenic	Classic
	5**	NPC1	c.3104C>T	p.Ala1035Val	Homozygous	Pathogenic	Classic
	6	NPC1	c.3104C>T	p.Ala1035Val	Compound heterozygous	Pathogenic	Classic
			c.1990G>A	p.Val1664Met		Pathogenic	
Juvenile	7	NPC1	c.3493G>A	p.Val1165Met	Homozygous	Pathogenic	Variant
	8	NPC1	c.1114C>T	p.Arg372Trp	Compound heterozygous	Pathogenic	Classic
		NPC1	c.3104C>T	p.Ala1035Val		Pathogenic	
	9	NPC1	c.3019C>G	p.Pro1007Ala	Homozygous	Pathogenic	Variant
	10	NPC1	c.3104C>T	p.Ala1035Val	Compound heterozygous	Pathogenic	Variant
			c.2292G>A	p.Ala764Ala		Pathogenic	
Adult	11	NPC1	c.3548G>A	p.Arg1183His	Homozygous	VUS*	Variant

*VUS, variant of uncertain significance, **Siblings.

Discussion

This case series highlights the broad phenotypic diversity observed in patients with NPC, corroborating the main genotypes previously described in the literature. The symptoms of the patients ranged from neonatal systemic manifestations to neuropsychiatric impairments in adolescence. Of the five clinical presentation forms identified, four are represented in our sample, with infantile and juvenile forms predominating. These findings are consistent with those reported in previous studies conducted in European, Asian, and American populations [17-22].

Visceral abnormalities, along with the characteristic neurological and psychiatric manifestations of the disease, were clearly identified in all clinical forms evaluated in this study. Splenomegaly, either alone or in combination with hepatomegaly, stands out as a significant indicator of the disease, although it may be absent in up to 10% of cases [8,13,23]. Except for the adult form, all patients showed splenomegaly, and most also had hepatomegaly. Splenomegaly was observed to precede hepatomegaly and was detected in the early infantile form during the first year of life, indicative of the typical progression of NPC [8]. On the other hand, prolonged jaundice or cholestasis was observed in all cases of early infantile NPC and in two cases of the juvenile form, underscoring a higher prevalence of cholestasis in patients under 6 years old [8,24].

Among the neurological symptoms observed, vertical supranuclear gaze palsy was present in all cases of the study population. This symptom manifests in approximately 65% of patients with NPC and, when present together with gelastic cataplexy, is considered a strong predictor of the disease [8,25].

Unlike vertical gaze palsy, gelastic cataplexy—a loss of postural tone triggered by emotional stimuli—is a relatively rare sign that can be mistaken for falls or cerebellar ataxia [8,16]. In our study, only one patient exhibited this symptom, highlighting its rarity.

Cerebellar ataxia, along with dysphagia and dysarthria, formed the second most common group in our sample, present in 10 of the 11 cases described. Cerebellar ataxia is a moderate indicator of the disease, but in association with other symptoms, it becomes strongly suggestive of NPC, especially when associated with dysphagia, dysarthria, and dystonia [25]. Ataxia generally appears after dystonia, and in patients with infantile and juvenile clinical presentations, the reverse may occur [8]. In our series, all patients with these signs developed ataxia before dystonia.

On the other hand, epilepsy, although not specific to NPC, can be considered an auxiliary indicator of disease progression. It is more commonly observed in the infantile and juvenile clinical forms, as evidenced in our population [1]. Conversely, the myoclonic jerks reported in three of the patients are not characteristic of NPC and could be related to a type of epileptic seizure or movement disorder [1,26].

The natural history of NPC includes progressive physical disability, evidenced by muscle weakness and/or spasticity, along with delayed or lost neuropsychomotor developmental milestones [27]. In our series, cognitive decline was primarily observed compared to psychiatric symptoms. However, it is important to emphasize that the reported behavioral disorders may mask the presence of psychiatric disorders.

According to the International Consensus on the Registration and Treatment of NPC Disease [10], a laboratory algorithm is recommended in cases where there is clinical suspicion of Niemann-Pick type C (NPC) disease. This algorithm employs biochemical markers as screening tools, which include quantifications of oxysterols, lysosphingolipids, and bile acids, either individually or in combination. Our results demonstrated that both cholestantriol (an oxysterol) and Lyso-SM-509 (a lysosphingolipid) tested positive, either singly or in combination, in 9 out of the 11 patients, thereby confirming their specificity and sensitivity as diagnostic tools for NPC disease, as previously reported [28,29].

In patients with high clinical suspicion and/or a biomarker profile consistent with NPC, genetic confirmation is mandatory. In our cases, analysis of the NPC1 and NPC2 genes revealed mutations only in the NPC1 gene, which is consistent with the literature indicating a higher prevalence of pathogenic variants in this gene compared to NPC2 [30-31]. The most frequent mutation in NPC1 in our series was c.3104C>T (p.Ala1035Val), found in 8 of the 11 patients, confirming the high frequency of this mutation in the southeastern region of Brazil [29] and its independence from the clinical presentation form. In 4 of these patients, this variant was present in homozygous state (2 siblings), while in the others, it was in compound heterozygosity with other mutations also described in the Brazilian series [18,32]. Additionally, the NPC1: c.3548G>A variant, found in the only patient with adult-onset NPC, has been classified as of uncertain pathogenic significance in the databases to date.

Complementarily, and in cases of inconclusive results, the Filipin test is performed [10]. In this study, all patients underwent skin biopsy for Filipin analysis, facilitated by the availability of a national Brazilian program dedicated to NPC diagnosis. Of the 6 patients with a 'classic' staining pattern, 5 presented the NPC1: c.31014C>T mutation, suggesting a possible correlation between this variant and the observed biochemical pattern, as previously described [33]. Additionally, 5 patients showed a 'variant' staining pattern in the Filipin test, indicative of moderate alterations in the biochemical phenotype, without a clinically established correlation [15].

Regarding the MRI findings, all patients presented alterations such as cerebral and cerebellar atrophy or demyelination, indicative of involvement in cortical and subcortical morphology, which is consistent with findings from previous studies [34,35]. However, it is important to note the lack of specific imaging findings that could contribute to the suspicion index of NPC [25] and clinical follow-up [36].

All patients received substrate reduction therapy with miglustat. Although the observational nature of this study limits the generalizability of treatment responses, changes in scale scores could provide some insights. For those initially scored as having mild disability (5-8 points) -except for case 7-, there was a slower progression in the disability scale throughout the follow-up period, advancing only to 8-9 points. This finding aligns with data suggesting that patients exhibiting lower rates of neurological deterioration at the onset of treatment tend to respond more favorably than those with more rapid progression rates [18,37]. These findings suggest that, in our cases, miglustat may have the potential to stabilize or possibly mitigate the progression of disability in patients with milder initial symptoms, consistent with observations made in other populations [22,37].

Our study presents some limitations, the primary of which is the retrospective nature of our data collection, based solely on historical information available in medical records. For instance, there was an incomplete characterization of respiratory complications, inadequate information on the adverse effects of miglustat, and insufficient details regarding the causes of loss to follow-up. Future studies should aim to address these gaps by employing prospective methodologies, improving data collection on adverse effects and patient compliance, and conducting more comprehensive systematic evaluations.

Conclusion

This study on NPC in Brazil provides a broader perspective on the clinical, biochemical and molecular presentation of the disease. The most common neurological manifestations included vertical gaze palsy, ataxia, dysarthria, and dysphagia, as well as behavioral changes and progressive cognitive decline. These symptoms, combined with visceromegaly, are sufficient indicators to initiate the investigation of NPC. Biomarker screening tests and genetic analyses not only confirm the diagnosis but also facilitate the exploration of diverse genotypic profiles within the population.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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