



## Niemann–Pick C disease in Spain: Clinical spectrum and development of a disability scale

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### Abstract

**Objectives:** To describe the clinical evolution of Niemann–Pick C disease to identify possible factors involved in the diagnosis and severity of the disease.

**Methods:** A clinical database and a severity scale was created to evaluate 45 patients diagnosed with Niemann–Pick type C in the last 28 years in Spain.

**Results:** Complete clinical data were obtained from 30 patients, all were confirmed to have mutations in the *NPC1* gene. Regarding clinical form, 3 were perinatal, 7 severe infantile, 6 late infantile, 11 juvenile and 3 adult. Biochemical phenotype was classic in 26. Splenomegaly was present in 28 patients (93%) with a wide range of age at detection. The first symptom of neurological disease was clumsiness, followed in 2–4 years by cerebellar signs. Ophthalmoplegia appeared 2–4 years later and became complete 1–2 years after onset. Dysarthria appeared by the time of complete ophthalmoplegia. Diagnosis was made before the onset of neurological signs in patients with the severe infantile form, at the time of onset of cerebellar signs in the late infantile form and complete ophthalmoplegia in late onset forms.

**Conclusions:** In our series, splenomegaly is present in 96% of patients, even in late onset forms during the first years of life. Clumsiness in children with otherwise normal motor development precedes the onset of ataxia by 2–4 years in Niemann Pick type C. A disability scale could be useful for monitoring evolution, establishing possible phenotypic correlations and evaluating future therapies.

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**Keywords:** Niemann Pick C; Phenotype; Clinical delineation; Database and disability scale

### 1. Introduction

Niemann–Pick disease type C (NPC [MIM 257200 and MIM 601015]) is an autosomal recessive lipid-storage disorder characterized clinically by the presence of hepatosplenomegaly and severe progressive neurological dysfunction with varying age at onset and in the subsequent course of the disease [1,2]. At the cellular level the disease produces a late-endosomal/lysosomal accumulation of endocytosed

unesterified cholesterol that leads to the accumulation of a complex pattern of lipids in non-neural tissues and in the brain [2]. The severity of the cellular cholesterol lesion varies widely, with typical severe alterations described as the ‘classic’ biochemical phenotype and mild alterations as the ‘variant’ phenotype [3].

Genetic and allelic heterogeneity was established for this disease by the identification of two different genes, *NPC1* and *NPC2* [2,4,5,8]. *NPC1* gene is affected in 95% of the NPC families. The finding of identical cellular and products may function either in tandem or sequentially [5]. Although the exact function and role in intracellular trafficking of cholesterol and glycolipids remains unknown, recent data biochemical phenotypes in NPC patients with lesions in different genes led to the

*Abbreviations:* NPC, Niemann–Pick disease type C; SI, severe infantile form; LI, late infantile form.

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Table 1  
Clinical database

1. Examination date
2. Name and surname
3. Date and place of birth
4. Name of attending physician
5. Age at examination
6. Age at diagnosis
7. Consanguinity
8. Other members of the family affected by NPC
9. Pregnancy
10. Delivery
11. Weight at birth
12. Ascitis at birth
13. Neonatal jaundice
14. Duration
15. Phototherapy
16. Splenomegaly
17. Hepatomegaly
18. Neonatal hypotonia
19. Early psychomotor development
20. Clumsiness
21. Learning delay
22. Ataxia
23. Dysmetria
24. Vertical ophthalmoplegia
25. Complete ophthalmoplegia
26. Dystonia
27. Dysarthria
28. Cataplexy age at detection
29. Pyramidal signs
30. Dysphagia
31. Nasogastric tube/gastric button feeding
32. Seizures
33. Treatment
34. Controlled epilepsy
35. Psychiatric disturbances
36. Type of psychiatric disturbances
37. Psychiatric treatment
38. Sleep disturbances
39. Treatment of sleep disturbances
40. Age of death
41. Biochemical form
42. Molecular study
43. Brain MRI atrophy
44. Brain MRI white matter abnormalities
45. Bone marrow, foam cells
46. Bone marrow, sea-blue histiocytes
47. Skin biopsy
48. Ophthalmological exam
49. Abdominal ultrasound hepatomegaly size in centimeters
50. Abdominal ultrasound splenomegaly size in centimeters
51. Clinical form

conclusion that both genes suggest that NPC1 protein [6] interacts with NPC2 [7]. The *NPC2* gene (MIM 601015), caused by mutations in the previously recognized *HE1* gene, accounts for 5% of families with NPC [8,9]. From a clinical point of view, the classic symptoms and signs of NPC are present. Although non-specific, pronounced lung involvement is prominent in some of the families reported, with good phenotype–genotype correlation in the families described [9].

In this report, we present clinical and biochemical data from 30 Spanish patients with NPC. The exhaustive collection of clinical data allowed us to accurately establish the chronological evolution and severity of the disease in its different forms.

## 2. Subjects, materials and methods

During the period 1975–2003, the clinical diagnosis of NPC in 45 patients (42 unrelated families) was biochemically confirmed in skin fibroblast cultures by demonstration of intralysosomal storage of unesterified cholesterol using filipin staining with methods previously described [3,10]. The classic biochemical phenotype includes patients with a striking accumulation of free cholesterol in lysosomes assessed by filipin staining while cells from biochemically ‘variant’ patients show only mild changes. In these variant cases, measurement of cholesterol esterification was performed. Molecular studies were performed on all patients except for one case in which DNA was not available.

A clinical database with 51 items (three answers per item—Yes, No and Unknown—and if Yes, age at detection) was created to record the age at onset of the main clinical symptoms and signs of the disease, age at diagnosis and the results of diagnostics tests performed for each patient (Table 1). Classification of patients with respect to their clinical and biochemical characteristics was as previously proposed [1,3,11]. Neurological patients were categorized by type and age at onset of first symptoms into either a severe infantile (SI) form (onset at age <2 years), a late infantile (LI) form (onset at age 3–5 years), a juvenile form (onset at age 5–16 years) or an adult form (onset at

Table 2  
Disability scale

1. Ambulation	Score	3. Language	Score
Normal	1	Normal	1
Autonomous ataxic gait	2	Mild dysarthria (understandable)	2
Outdoor assisted ambulation	3	Severe dysarthria (only comprehensible to some members of the family)	3
Indoor assisted ambulation	4	Non-verbal communication	4
Wheelchair-bound	5	Absence of communication	5
2. Manipulation	Score	4. Swallowing	Score
Normal	1	Normal	1
Slight dysmetria/dystonia (allows autonomous manipulation)	2	Occasional dysphagia	2
Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)	3	Daily dysphagia	3
Severe dysmetria/dystonia (requires assistance in all activities)	4	Nasogastric tube or gastric button feeding	4

age >16 years). We included in the ‘perinatal’ form those patients who died from liver failure in the first months of life.

A disability scale was also created containing the four main functional areas (Table 2) in evaluating the severity of the disease. The aim of our study was to describe the chronological evolution of the disease. The exact age at onset of the main symptoms and signs was considered as essential, so we excluded in the present report those patients ( $n=15$ ) for whom these data were not available.

### 3. Results

Complete clinical data were obtained from 30 patients (17 girls) with ages ranging from 4 days to 35 years. There was positive familial history in four patients, of whom three had an affected sibling and one an affected first cousin.

#### 3.1. Clinical and biochemical forms

Three patients presented with the ‘perinatal’ form, seven with the SI form, six with the LI form, eleven with the juvenile form and three with the adult form. Regarding the biochemical phenotype, 26 (87%) patients belonged to the classic phenotype and 4 (13%) to the variant phenotype. The classic biochemical phenotype was found in all clinical forms while the variant phenotype was associated either with the juvenile (3/11 patients) or the adult form (1/4 patients).

Molecular analysis showed mutations in the *NPC1* gene in all patients studied [12].

#### 3.2. Clinical symptoms and signs

Jaundice was present in all perinatal and SI cases, in 33% of patients with LI form, and in 46% of cases with juvenile form; it was absent in adults. Splenomegaly was present in

28 patients (93%) with a wide range of age at detection, especially in late onset forms. Of the two patients without splenomegaly, one presented with juvenile form and the other with adult form. Hepatomegaly was detected in 86% of patients presenting with SI form, 83% with LI form, and 46% with juvenile form; it was absent in the adult form. In general, hepatomegaly was detected at the same time as splenomegaly. Early psychomotor development was abnormal in all SI cases and normal in all the other neurological forms.

The median age and age range at onset of the main clinical symptoms and signs in different neurological phenotypes are shown in Table 3. Cataplexy was present in 67% of patients with SI form, 40% with LI form, and 30% with juvenile form; it was absent in the adult form. Epilepsy appeared in 33% of patients with SI form, 67% of LI form patients, and 55% of juvenile patients; it was not present in adults. It was usually well controlled with only one antiepileptic drug.

Bone marrow biopsy was performed in all the patients (except in one sibling) when the diagnosis was clinically suspected that showed foam cells and/or sea-blue histiocytes. Brain MRI was either normal or showed alterations in the form of white matter changes and/or cerebellar/cerebral atrophy. As MRI was performed at a different age in each patient, it is difficult to extract significant data.

The evolution of the disease in terms of age at onset of the main symptoms and signs and diagnosis in the different forms is also shown in Fig. 1A–D. The median age at diagnosis in the severe infantile form preceded the onset of neurological signs. In the late infantile form the median age at diagnosis coincides with the age at detection of cerebellar signs, and in the juvenile form the median age at diagnosis coincides with age at detection of complete vertical ophthalmoplegia.

In the case of the adult patients, two presented psychiatric disturbances in the form of hallucinations or psychotic

Table 3

Age at detection of the main symptoms and signs in each clinical form

	Severe infantile 7 patients	Late infantile 6 patients	Juvenile 11 patients	Adult 3 patients
Splenomegaly	<b>Birth</b> (Birth–2 years)	<b>3 months</b> (Birth–7 years)	<b>7 years</b> (1 month–16 years)	<b>24 years</b> (19–30 years)
Hepatomegaly	<b>Birth</b> (Birth–2 years)	<b>2 months</b> (Birth–5 years)	<b>10 years</b> (5 months–16 years)	
Clumsiness	<b>1 year</b> (1–2 years)	<b>2.5 years</b> (1.5–4 years)	<b>6 years</b> (3–10 years)	<b>13 years</b>
Learning delay		<b>4 years</b> (3–4 years)	<b>6 years</b> (4–10 years)	<b>10 years</b> (10–16 years)
Ataxia	<b>1.5 years</b> (1–2 years)	<b>5 years</b> (3–5 years)	<b>9 years</b> (5–14 years)	<b>19 years</b> (17–33 years)
Dysmetria	<b>2 years</b> (1–2 years)	<b>5 years</b> (4–6 years)	<b>9.5 years</b> (7–14 years)	<b>19 years</b> (18–33 years)
Onset VO	<b>2 years</b> (1–2.5 years)	<b>5.5 years</b> (4–6 years)	<b>10 years</b> (7–22 years)	<b>26.5 years</b> (19–34 years)
Complete VO	<b>3 years</b>	<b>6.5 years</b> (6–8 years)	<b>11 years</b> (7–16 years)	<b>22 years</b>
Dystonia	<b>2 years</b> (2–2.5 years)	<b>8 years</b> (4–8 years)	<b>11 years</b> (10–15 years)	<b>26 years</b> (18–34 years)
Dysarthria	<b>2 years</b> (2–2.5 years)	<b>7 years</b> (5–7 years)	11 years (7–19 years)	<b>28 years</b> (22–34 years)
Cataplexy	<b>2.5 years</b> (2–3 years)	<b>5.5 years</b> (5–6 years)	<b>16 years</b> (15–19 years)	
Dysphagia	<b>2 years</b> (1–3.5 years)	<b>8.5 years</b> (5–9 years)	<b>14 years</b> (10–19 years)	<b>29.5 years</b> (28–31 years)
NGF/gastric button	<b>3 years</b> (1.5–4.5 years)	<b>8 years</b> (6.5–10 years)	<b>15.5 years</b> (14–17 years)	
Epilepsy	<b>1.5 years</b> (1–2 years)	<b>8 years</b> (5–9 years)	<b>10 years</b> (9–16 years)	
Death	<b>4 years</b> (3.5–5 years)	<b>11 years</b> (7–15 years)	<b>16 years</b> (11–21 years)	
Diagnosis	<b>1.5 years</b> (3 months–3 years)	<b>5 years</b> (6 months–7 years)	<b>11 years</b> (1.5–23 years)	<b>24 years</b> (20–30 years)

VO: vertical ophthalmoplegia; NGF: nasogastric tube feeding.

In bold type, median age at detection; in brackets, age range at detection.

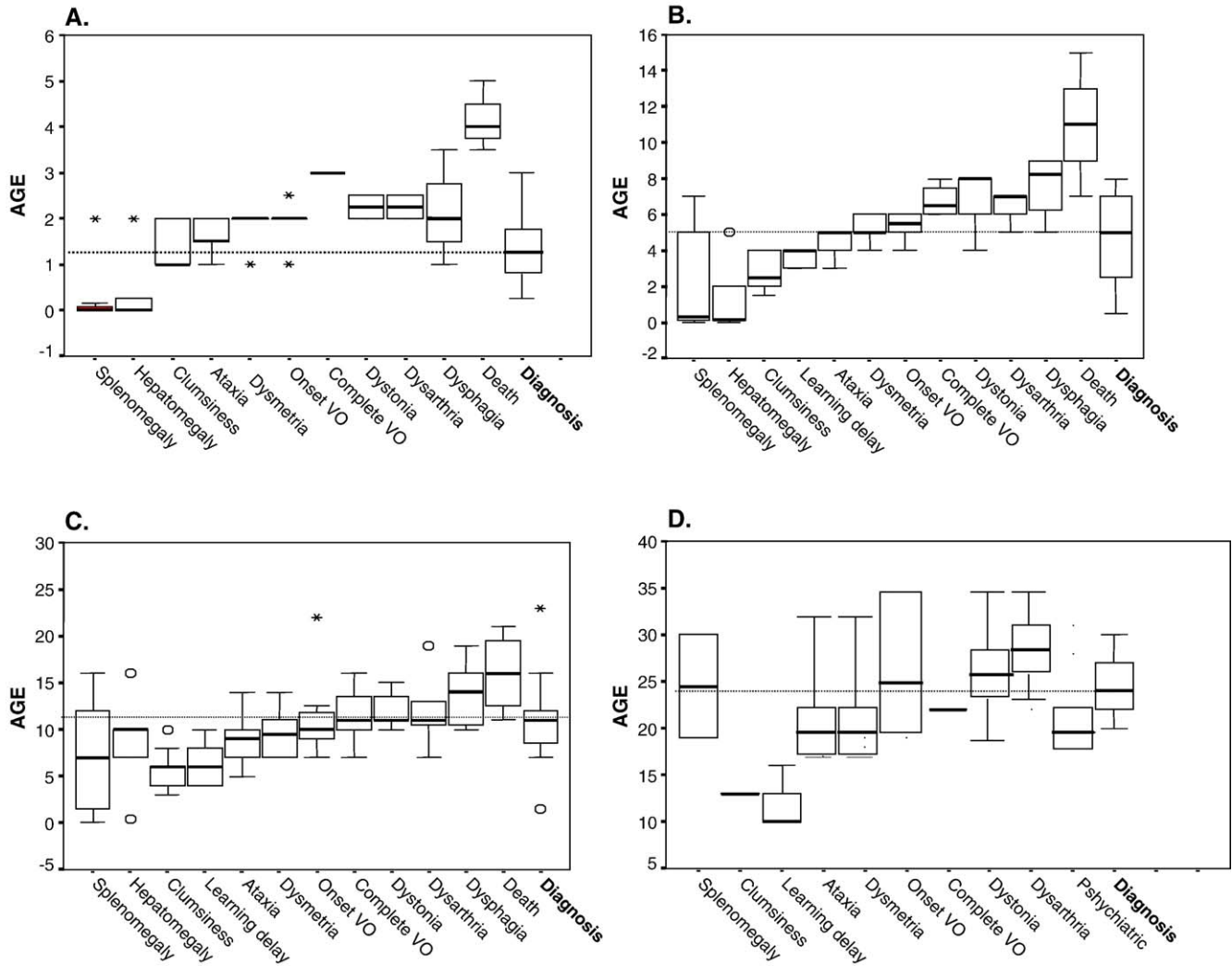


Fig. 1. (A) Early infantile. (B) Late infantile. (C) Juvenile. (D) Adult forms. Box plot representation of the detection of the main symptoms and signs in relation to the age of diagnosis (dotted line) in the different clinical forms. The length of the boxes indicates the interquartile space (P25–P75); the horizontal line into the box represents the median (P50) and the whiskers indicate the adjacent values. The circles indicate the outliers and the star represents an extreme value.

episodes as the first symptom of the disease. In one of the patients the diagnosis was made by detection of splenomegaly before the onset of neurological symptoms (her younger sister, suffering from a juvenile form of the disease, had been diagnosed one year earlier). The other patient had no spleno/hepatomegaly, and neurological symptoms developed 4 years after the psychiatric disorder. Diagnosis was made when dysarthria and complete ophthalmoplegia were detected. The other patient showed no psychiatric disturbances, while developing progressive neurological disease from the age of 19 years. Diagnosis was made at the time of onset of vertical ophthalmoplegia. At the time of finishing this report, these patients were still alive at 35, 32 and 32 years of age, respectively.

The disability scale created as a means of evaluating the severity of the disease showed, as expected, higher scores at earlier ages in early onset forms (Table 4). In the juvenile form, the scores increased rapidly from the age of 16 years, but interestingly, the 4 patients with mild cellular cholesterol

alterations (the variant form) showed much lower scores at that age than did the patients with severe cellular cholesterol alterations (classic ones) (Fig. 2).

#### 4. Discussion

The frequency of the juvenile form of Niemann–Pick type C in our series (37%) is lower than that reported for a series in a neighboring country, Portugal [13], in which the juvenile presentation accounted for 67% of the patients. In contrast, the severe infantile form was found with a frequency similar to that reported in the Portuguese series and in several previously reported series from Europe, Middle East and North Africa.

With respect to the clinical signs, the presence of neonatal jaundice was found to be related to the clinical form. In one report [14], NPC was found to be the most frequent metabolic disorder presenting with neonatal cholestasis (7.5% of all infants evaluated for cholestasis).

Splenomegaly appears as an almost constant visceral sign independently of the clinical form. It is important to note that this sign is present even in late onset neurological forms during the first years of life (from 1 month of age in our series in the juvenile form) [15]. Screening for NPC should be mandatory in infants with splenomegaly of unknown origin in order to avoid delayed diagnosis and the risk to undiagnosed siblings of NPC patients. As in the case of jaundice, hepatomegaly appeared to be related to clinical form, as previously reported [3].

Patients with the severe infantile form are characterized by the presence of abnormal early psychomotor development followed rapidly by the appearance of the rest of the symptoms between the first and the second years of life. In these cases, early diagnosis is the rule even in the absence of neurological signs. In the other clinical forms, the first sign of the disorder is the onset of an insidious clumsiness in children with otherwise normal psychomotor development. This should be a red flag and a second chance for early diagnosis since, according to our data, it precedes the onset of overt cerebellar ataxia by 2–4 years. In any case, despite these warning symptoms and visceral signs, or even in the presence of overt ataxia, the diagnosis of late onset forms of NPC is often delayed until the detection of vertical ophthalmoplegia, which is generally considered a characteristic hallmark of the disease. Vertical ophthalmoplegia appears 2–4 years after the cerebellar signs, and it becomes completely shorter after onset. At this time, signs of brain stem disease appear

Table 4  
Scores of the disability scale in the different clinical forms

Clinical form	Age years	Disability scale
Severe inf	3	18
Severe inf	3	18
Severe inf	3, 5	17
Severe inf	4	18
Severe inf	4	15
Severe inf	4	18
Severe inf	3	16
Late inf	10	17
Late inf	7	18
Late inf	3	4
Late inf	8	10
Late inf	10	18
Late inf	10	16
Juvenile V	11	7
Juvenile V	10, 5	10
Juvenile V	13	8
Juvenile	12	8
Juvenile V	16	8
Juvenile	6	4
Juvenile	16	17
Juvenile	18	17
Juvenile	12	16
Juvenile	7	6
Juvenile	28	14
Adult	31	16
Adult	33	10
Adult	32	16

V: variant form.

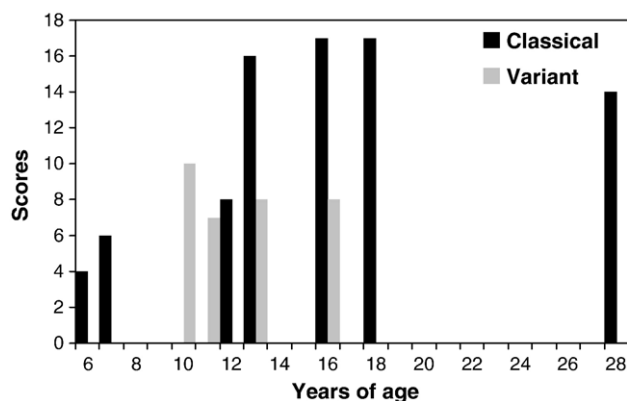


Fig. 2. Disability scale applied to the juvenile form comparing the patients with mild cellular cholesterol transport dysfunction (biochemical variant form) that have lower scores, to the patients with severe cellular free cholesterol accumulation in lysosomes by filipin staining (biochemical classical form) with higher scores.

(dysarthria), followed 2–4 years later by dysphagia, and death occurs approximately 1–2 years later. In adult patients, diagnosis of NPC can be even more difficult, as some cases may present with psychiatric disturbances, as did two of our patients and others reported in the literature [16,17]. It is important to note that in our series splenomegaly was not detected in two adult patients and some juvenile and late infantile patients until the presence of ophthalmoplegia raised suspicion. This would imply that this sign is underdiagnosed since, as shown above, splenomegaly appears early in life even in late onset forms [16,17].

The higher frequency of cataplexy found in early onset forms in our series is related to the evolution of the disease since it appears in relation to the onset of brain stem dysfunction, as previously reported by other authors [18].

Because of the small size of the sample, only limited information can be extracted from the results of the scores of our disability scale. Even our observations of a lower score in patients with a mild cellular cholesterol transport dysfunction (biochemical variant form), compared to patients with a severe cellular cholesterol accumulation (biochemical classical form) (Fig. 2), would need to be tested on a larger cohort. Nevertheless, in line with scoring systems proposed earlier in several rare and phenotypically heterogeneous diseases such as Gaucher disease [19] and X-linked adrenoleukodystrophy [20,21], we believe that a consensual scale would be of invaluable help for a more accurate follow-up of the disease course in individual NPC patients. This would set up a basis for establishing more refined correlations between genotype and phenotypes, and above all, for monitoring the usefulness of future treatments.

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