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Differences in Niemann-Pick disease Type C symptomatology observed in patients of different ages

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ABSTRACT

Background: Niemann-Pick disease Type C (NP-C) is a genetic lipid storage disorder characterised by progressive neurovisceral symptomatology. Typically, disease progression is more pronounced in patients with early onset of neurological symptoms. Heterogeneous clinical presentation may hinder disease recognition and lead to delays in diagnosis. Here we describe the prevalence of signs and symptoms observed in patients with NP-C and analyse the relationship between these symptoms in different age groups.

Methods: The combined patient cohort used in the analyses comprised NP-C cases (n = 164) and controls (n = 135) aged 0 to 60 years from two previously published cohorts; a cohort of all ages from which patients ≤4 years of age were excluded and a cohort with early-onset NP-C and age-matched controls. The analysis of relationships between different signs and symptoms was performed for both NP-C cases and controls in two sub-groups, ≤4 and >4 years of age, using cluster analyses. The threshold of 4 years of age was selected to reflect the minimum age cut-off for satisfactory discriminatory power of the original NP-C SI. To assess the prevalence of individual signs and symptoms at age of diagnosis, patients were categorised by age into 5-year sub-groups, and prevalence values estimated for each sign and symptom of NP-C.

Results: Two main clusters of symptoms were clearly defined for NP-C cases in each age sub-group, whereas clusters were not as clearly defined for controls. For NP-C cases ≤4 years of age, one cluster comprised exclusively visceral symptoms; the second cluster combined all other signs and symptoms in this age group. For NP-C cases >4 years of age, each cluster contained a mixture of visceral, neurological and psychiatric items. Prevalence estimations showed that visceral symptoms (*e.g.* isolated unexplained splenomegaly) were most common in NP-C cases ≤4 years of age. Neurological symptoms were generally more common in NP-C cases >4 years of age than in younger patients, with the exception of hypotonia and delayed developmental milestones.

Conclusions: These analyses provide a comprehensive overview of symptomatology observed in a large combined cohort of patients with NP-C and controls across a wide range of ages. The results largely reflect observations from clinical practice and support the importance of multi-disciplinary approaches for identification of patients with NP-C, taking into account age-specific manifestations and their possible correlations.

1. Introduction

Niemann-Pick disease Type C (NP-C) is a neurodegenerative lipid storage disorder caused by mutations in either the *NPC1* (OMIM: *607623) or *NPC2* (OMIM: *601015) genes [1,2]. NP-C is characterised by a wide range of visceral, neurological and psychiatric symptoms that can vary considerably between patients [3]. It has been shown that visceral symptoms, in particular splenomegaly and prolonged neonatal jaundice, are among the most common symptoms in patients <4 years of age, whereas neurological and psychiatric symptoms are predominant in older children and adolescents (4–16 years of age), and adults (>16 years of age) [4]. A number of neurological symptoms, including vertical supranuclear gaze palsy (VSGP), dystonia, ataxia and

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dysphagia/dysarthria, are frequently observed in patients with NP-C > 4 years of age [4].

Referral for diagnostic testing in NP-C is dependent on recognition of the signs and symptoms of NP-C. However, detection can be difficult due to the extremely heterogeneous clinical presentation and generally low awareness of the disease among physicians [5]. The variable age of disease onset and wide range of manifestations complicate and delay the diagnosis and may be responsible for under-detection of NP-C and, in some cases, its misdiagnosis [5]. The NP-C Suspicion Index (SI) was developed to aid clinicians in the initial identification of patients who warrant diagnostic testing for NP-C [6–8]. Whilst advances are being made in screening for and diagnosing this disease, with new techniques showing great promise [9–14], a clearer description of the concurrent signs and symptoms and their prevalence at different ages may support initial detection of patients suspected of having NP-C, and ultimately aid diagnosis.

This manuscript provides an overview of the symptomatology observed in a cohort of patients with NP-C, evaluating relationships between signs and symptoms, and their prevalence at diagnosis in patients of different ages. The results of these analyses will be considered in light of observations from expert clinical practice, particularly with regard to the origin and nature of certain symptom clusters in different age groups.

2. Methods

2.1. Patient population

The pooled cohort used for the current analyses comprised two cohorts of NP-C cases and controls without NP-C, assessed in two studies for the development and validation of the original and early-onset NP-C SIs, as described previously [6–8]. Data for each cohort were collected from retrospective chart reviews of NP-C cases and controls. A diagnosis of NP-C was confirmed by filipin staining of cultured skin fibroblasts and/or *NPC1* and *NPC*2 sequencing. Controls were recruited from the same specialist referral centres and had one characteristic presentation of NP-C, but no suspicion of NP-C [6,8].

2.2. Ethics, consent and permissions

All patient data were blinded by the experts so that names, addresses or other identifying information were not available to any other party involved in the analysis or review of the data [6,8]. Therefore, this study did not require approval by an Ethics Committee. All investigators complied with applicable local regulations and privacy laws to ensure patient confidentiality.

2.3. Signs and symptoms

Data on signs and symptoms of NP-C were collected using similar terms for both cohorts, adapted to include appropriate symptoms and terminology in patients ≤4 years. In the current analyses, data on the characteristic signs and symptoms of NP-C collected for the development of the original NP-C SI tool [6] were included for patients >4 years of age. For patients ≤4 years of age, the signs and symptoms recorded as part of the development of the early-onset NP-C SI were included [8]. Signs and symptoms for both age groups are detailed in Table 1.

Cluster analyses were performed using the signs and symptoms included in the original NP-C SI tool for patients >4 years of age and, for patients ≤4 years of age, using all items recorded in the early-onset cohort. For all patients, regardless of age, the prevalence analyses considered only those signs and symptoms included in the original NP-C SI.

Table 1
Signs and symptoms of NP-C.

	Items included in the original NP-C SI	Items recorded in the early-onset cohort
Visceral symptoms		
Prolonged unexplained neonatal jaundice or cholestasis	X	X
Hydrops foetalis	X	X
Siblings with foetal ascites	X	X
Isolated unexplained splenomegaly (historical or current) with or without hepatomegaly	X	X[a]
Hepatosplenomegaly	–	X
Splenomegaly	–	X
Direct bilirubinaemia	–	X
Foetal oedema or ascites	–	X
Low platelet count (<150 × 10^9/L)	–	X
Pulmonary infiltrates	–	X
Neurological symptoms		
VSGP	X	X
Ataxia, clumsiness or frequent falls	X	X
Dysarthria and/or dysphagia	X	X
Dystonia	X	X
Hypotonia	X	X
Myoclonus	X	X
Gelastic cataplexy	X	X
Acquired and progressive spasticity	X	X
Seizures	X	X
Delayed developmental milestones	X	X[b]
Language acquisition	–	X
Gross motor function	–	X
Fine motor function (manipulation)	–	X
Deterioration or loss of previously acquired physical skills	–	X
Hearing deterioration	–	X
Urinary and faecal incontinence (inappropriate to age)	–	X
Psychiatric symptoms		
Pre-senile cognitive decline and/or dementia (defined as mental regression in the early-onset cohort)	X	X
Disruptive or aggressive behaviour in adolescence and childhood	X	X[c]
Psychosis	–	X
Treatment-resistant psychiatric symptoms	X	X
Other psychiatric disorders	X	X
Psychotic symptoms (hallucinations, paranoid delusions and/or thought disorder)	X	–
Deterioration or loss of previously acquired mental skills	–	X
Deterioration of social interaction	–	X
Hyperactivity	–	X
Sleep disturbances	–	X
Other severe emotional disturbances (anxiety, crying, withdrawal, autistic disorder, *etc.*)	–	X
Family history		
Parent or sibling with NP-C	X	X
Cousin with NP-C	X	X
Consanguinity of parents	–	X

X, symptom/sign was recorded; –, symptom/sign was not recorded.
NP-C, Niemann-Pick disease Type C; SI, Suspicion Index; VSGP, vertical supranuclear gaze palsy.
[a] Presence of hepatosplenomegaly or splenomegaly was included as isolated unexplained splenomegaly (historical or current) with or without hepatomegaly in the early-onset cohort.
[b] Presence of either delayed language acquisition, gross motor function, or fine motor function (manipulation) were included as delayed developmental milestones in the early-onset cohort.
[c] Defined as disruptive or aggressive behaviour in the early-onset cohort.

2.4. Cluster analysis

For the cluster analyses, the pooled cohort from the two studies was divided into two age groups (≤4 and >4 years of age) based on current