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 NPC2 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 ($<150 \times 10^9$/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

age at data collection. The threshold of 4 years of age was selected because it reflects the minimum age cut-off for satisfactory discriminatory performance of the original NP-C SI (ROC AUC values were 0.562 for patients <4 years of age, 0.981 for patients >4–16 years of age, 0.964 for patients >16 years of age) [4]. Age at data collection was used for these analyses to ensure inclusion of a maximum number of patients. To avoid duplication of data, which may have resulted from patients being included in both individual cohorts, patients within the original NP-C SI cohort [6] with an age at data collection ≤4 years (NP-C cases, n = 13; controls, n = 9) were excluded from the combined cohort for the cluster analyses.

The individual signs and symptoms observed in NP-C cases (Table 1) were included as independent variables. Only items observed in ≥5% of NP-C cases or ≥5% of controls were included in the cluster analyses. Clusters were identified using Ward's method. The clustering process started with K clusters of size 1, where each variable was equivalent to one cluster. At each step, the two closest clusters were grouped. The process was repeated until all variables were included in one unique cluster. The proximity between clusters was measured by the semi-partial R^2, which reflects the increase in the proportion of variation explained by the clusters. Smaller semi-partial R^2 values are related to stronger relationships between the variables or clusters. Results are presented as a dendrogram in which clusters of variables can be identified by relative increases in the semi-partial R^2. Homogeneous differences in the semi-partial R^2 indicate a lack of clustering. The threshold of semi-partial $R^2 = 0.2$ for clusters was defined based on the dendrogram and expert opinion; sub-clusters were defined based on expert opinion.

2.5. Prevalence of individual signs and symptoms of NP-C at diagnosis in different age groups

In the exploratory prevalence analysis, the pooled cohort was categorised into eleven 5-year sub-groups, from 0 to 4 to ≥50 years of age, based on age at diagnosis (date of referral for a filipin staining test for NP-C cases; age at data collection for controls). Patients within the original NP-C SI cohort for whom age at diagnosis was unavailable, or who had an age at diagnosis of ≤4 years, were excluded from the analysis (NP-C cases, n = 25; controls, n = 43).

The prevalence of signs and symptoms of NP-C at diagnosis in each age group was calculated using generalised additive models. Data were fitted with the binomial distribution and the link logit. Age at diagnosis was included in the model using splines with 3 degrees of freedom. The model used to generate prevalence curves took into account all individual prevalence values calculated for each sign or symptom of NP-C at age at diagnosis. The exploratory prevalence curves represent smoothed estimates, which were calculated taking into account adjacent prevalence values.

Prevalence and cluster analyses were performed using SAS® Software (PROC GAM and PROC CLUSTER procedures, respectively) version 9.3.

3. Results

3.1. Patient population

The distribution of patients from the two studies is shown in Fig. 1. In total, 164 NP-C cases and 135 age-matched controls were included in the pooled cohort. Patient demographics are shown in Table 2.

3.2. Cluster analyses

The total pooled cohort population of 164 NP-C cases and 135 controls were included in the cluster analyses, and were split into two age groups: ≤4 years of age, 106 NP-C cases and 63 controls; >4 years of age, 58 NP-C cases and 72 controls (Table 2). The age cut off reflects
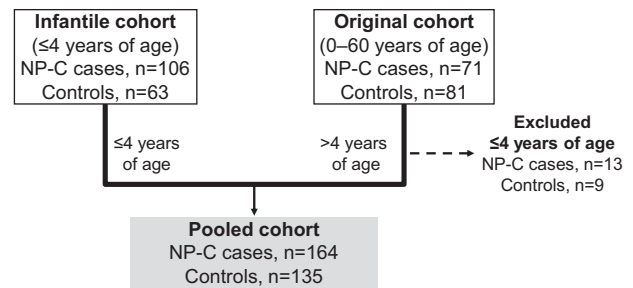

Fig. 1. Distribution of patients in the pooled cohort. n, total number of patients in the sub-group; NP-C, Niemann-Pick disease Type C.

the minimum age cut-off for satisfactory discriminatory performance of the original NP-C SI [4].

The clusters were not as clearly defined in the controls as in the NP-C cases in either of the two age groups. For controls, the differences in semi-partial R^2 values between branches of signs and symptoms in the dendrograms were broadly similar (Fig. 2 A and C).

For the NP-C cases, two very well defined clusters were observed in each age group (Fig. 2 B and D).
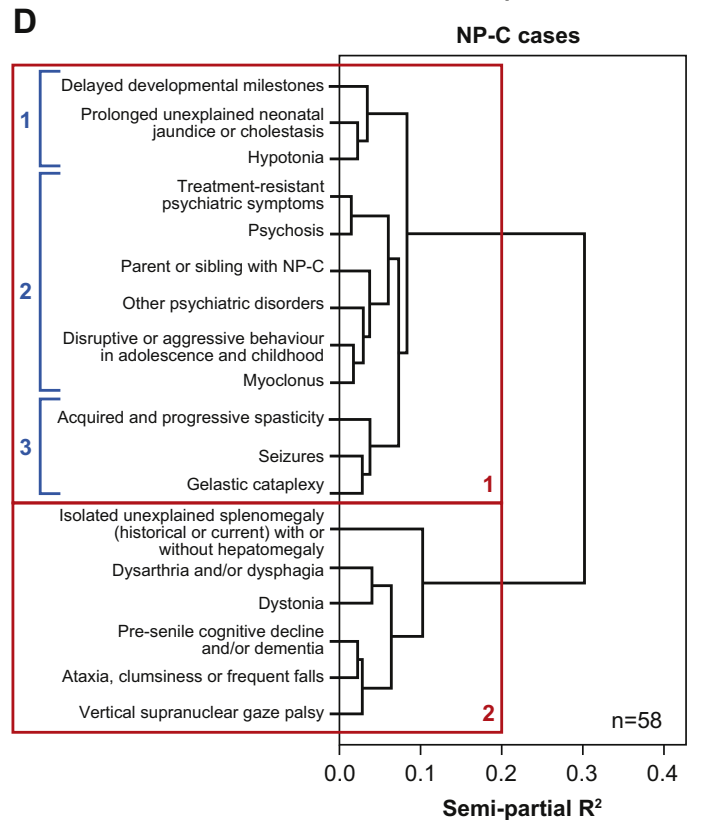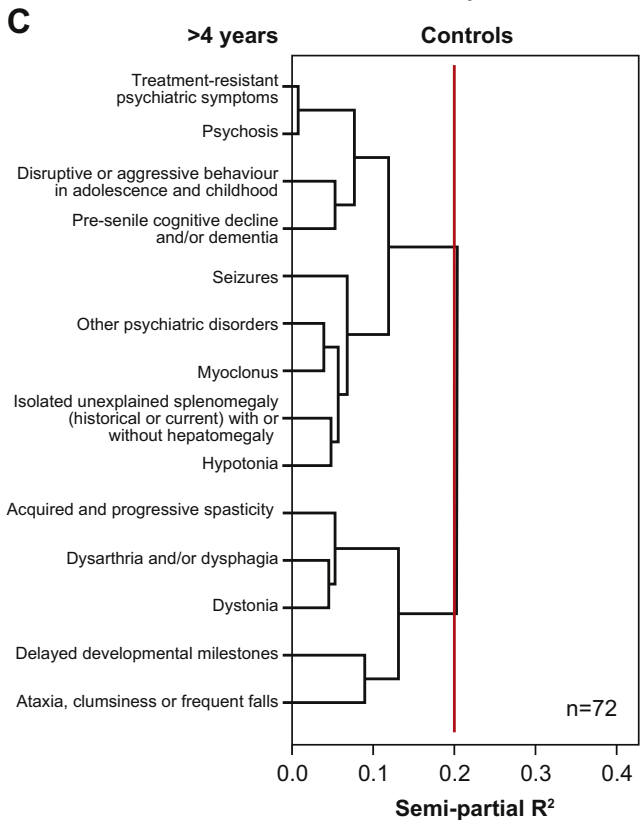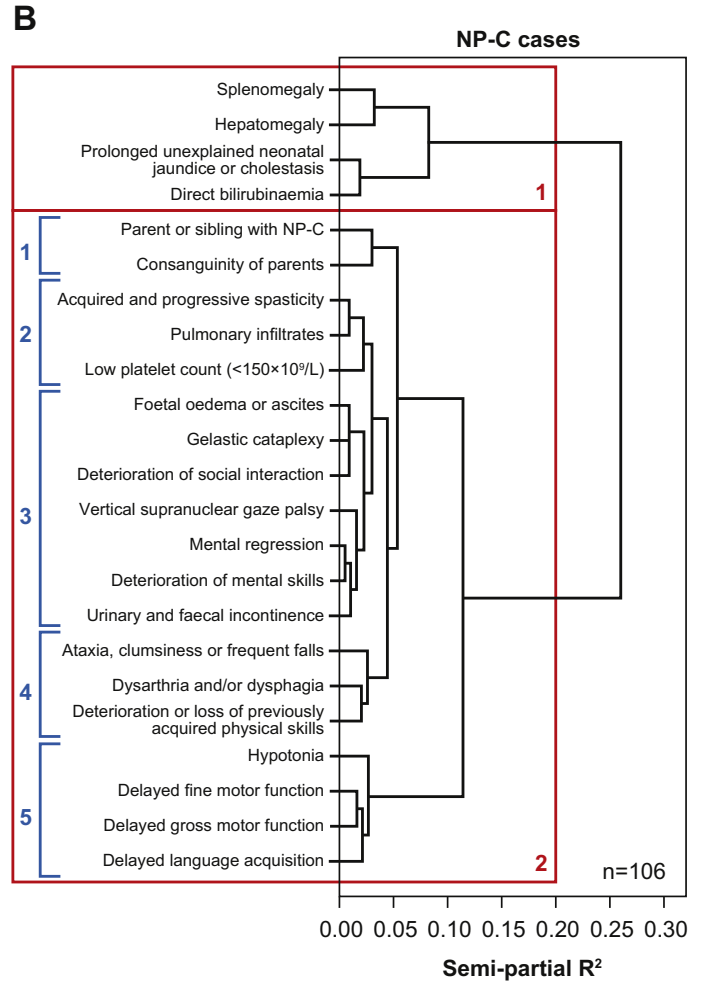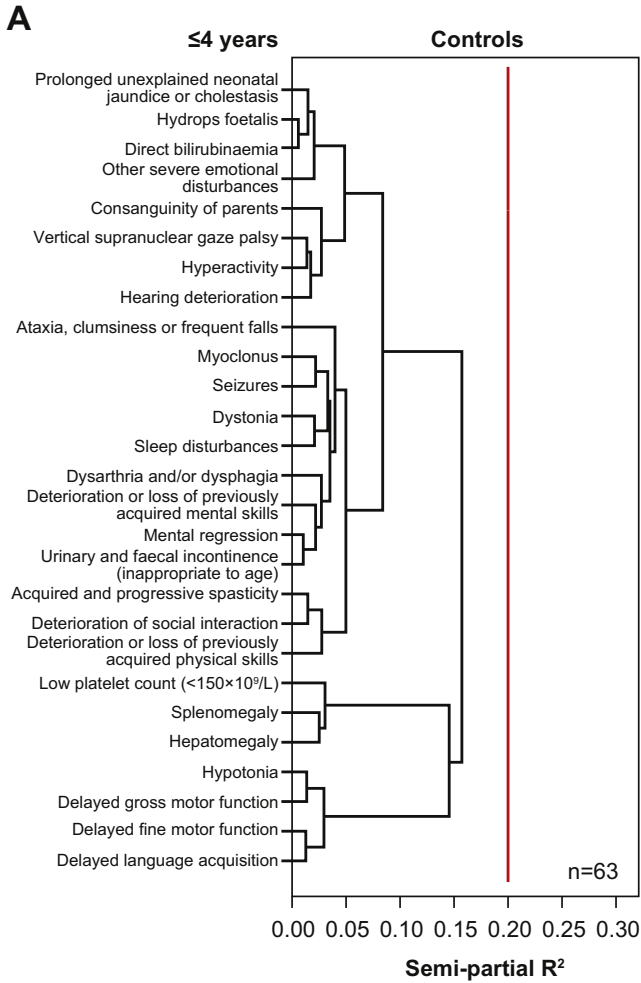
In NP-C cases ≤4 years of age, detailed investigation of the two well-defined clusters in relation to clinical experience revealed five lower-hierarchy sub-clusters within one main cluster (Fig. 2B). In general, the sub-clusters distinguishable in this age sub-group were considered to broadly reflect clinical observations. Clusters appeared to group visceral signs (cluster 1), family history (parents/siblings with NP-C and consanguinity of parents; sub-cluster 1), and classical, predominantly neurological signs, including VSGP and gelastic cataplexy (sub-cluster 3). More distinct cerebellar signs (ataxia, dysphagia/dysarthria, and deterioration of physical skills) also appeared clustered within a lower-hierarchy sub-cluster (sub-cluster 4). Non-specific visceral signs, pulmonary infiltrates and low platelet count, were clustered with spasticity (sub-cluster 2), as were further non-specific neurological symptoms (sub-cluster 5).

In patients >4 years of age, three lower-hierarchy sub-clusters were distinguishable, and appeared to represent non-specific symptoms

Table 2
Patient demographics.

	NP-C cases N = 164	Controls N = 135
Patients included in the cluster analysis		
≤4 years of age	n = 106	n = 63
Gender, n (%)		
Male	54 (51)	27 (43)
Female	52 (49)	36 (57)
Age (months)		
Mean (SD)	20.8 (16.7)	21.9 (14.2)
Median (minimum, maximum)	16.5 (0.0, 58.0)	23.0 (1.0, 48.0)
>4 years of age	n = 58	n = 72
Gender, n (%)		
Male	31 (53)	43 (60)
Female	27 (47)	29 (40)
Age (months)		
Mean (SD)	284.4 (162.6)	249.1 (178.6)
Median (minimum, maximum)	263.0 (64.0, 707.0)	178.0 (60.0, 661.0)
Patients included in the prevalence analysis	n = 152	n = 101
Gender, n (%)		
Male	80 (53)	49 (49)
Female	72 (47)	52 (51)
Age (months)		
Mean (SD)	98.4 (144.0)	103.1 (150.6)
Median (minimum, maximum)	36.0 (0.0, 619.0)	38.0 (1.0, 623.0)

N, total number of patients in the population; n, number of patients with recorded value; NP-C, Niemann-Pick disease Type C; SD, standard deviation.

A ≤4 years — Controls (n=63)

Features (top to bottom): Prolonged unexplained neonatal jaundice or cholestasis; Hydrops foetalis; Direct bilirubinaemia; Other severe emotional disturbances; Consanguinity of parents; Vertical supranuclear gaze palsy; Hyperactivity; Hearing deterioration; Ataxia, clumsiness or frequent falls; Myoclonus; Seizures; Dystonia; Sleep disturbances; Dysarthria and/or dysphagia; Deterioration or loss of previously acquired mental skills; Mental regression; Urinary and faecal incontinence (inappropriate to age); Acquired and progressive spasticity; Deterioration of social interaction; Deterioration or loss of previously acquired physical skills; Low platelet count (<150×10⁹/L); Splenomegaly; Hepatomegaly; Hypotonia; Delayed gross motor function; Delayed fine motor function; Delayed language acquisition. Semi-partial R^2 axis: 0.00–0.30.

B NP-C cases (n=106)

Cluster 1: Splenomegaly; Hepatomegaly; Prolonged unexplained neonatal jaundice or cholestasis; Direct bilirubinaemia. Subclusters 1–5: Parent or sibling with NP-C; Consanguinity of parents; Acquired and progressive spasticity; Pulmonary infiltrates; Low platelet count (<150×10⁹/L); Foetal oedema or ascites; Gelastic cataplexy; Deterioration of social interaction; Vertical supranuclear gaze palsy; Mental regression; Deterioration of mental skills; Urinary and faecal incontinence; Ataxia, clumsiness or frequent falls; Dysarthria and/or dysphagia; Deterioration or loss of previously acquired physical skills; Hypotonia; Delayed fine motor function; Delayed gross motor function; Delayed language acquisition. Semi-partial R^2 axis: 0.00–0.30.

C >4 years — Controls (n=72)

Features: Treatment-resistant psychiatric symptoms; Psychosis; Disruptive or aggressive behaviour in adolescence and childhood; Pre-senile cognitive decline and/or dementia; Seizures; Other psychiatric disorders; Myoclonus; Isolated unexplained splenomegaly (historical or current) with or without hepatomegaly; Hypotonia; Acquired and progressive spasticity; Dysarthria and/or dysphagia; Dystonia; Delayed developmental milestones; Ataxia, clumsiness or frequent falls. Semi-partial R^2 axis: 0.0–0.4.

D NP-C cases (n=58)

Cluster 1 (subclusters 1–3): Delayed developmental milestones; Prolonged unexplained neonatal jaundice or cholestasis; Hypotonia; Treatment-resistant psychiatric symptoms; Psychosis; Parent or sibling with NP-C; Other psychiatric disorders; Disruptive or aggressive behaviour in adolescence and childhood; Myoclonus; Acquired and progressive spasticity; Seizures; Gelastic cataplexy. Cluster 2: Isolated unexplained splenomegaly (historical or current) with or without hepatomegaly; Dysarthria and/or dysphagia; Dystonia; Pre-senile cognitive decline and/or dementia; Ataxia, clumsiness or frequent falls; Vertical supranuclear gaze palsy. Semi-partial R^2 axis: 0.0–0.4.

(sub-cluster 1), psychiatric symptoms (sub-cluster 2) and severe, advanced neurological manifestations (sub-cluster 3). The other main cluster (cluster 2) represented the classical presentation of NP-C, including splenomegaly/hepatomegaly, cognitive decline, and key neurological signs such as VSGP and ataxia (Fig. 2D).

3.3. Prevalence of signs and symptoms of NP-C by age at diagnosis

In total, 152 NP-C cases and 101 controls were included from the pooled cohort in the analysis. Patient demographics are shown in Table 2. To assess the prevalence of individual signs and symptoms of NP-C at diagnosis, patients were categorised based on age at diagnosis. Age distribution of all NP-C cases and controls used in the prevalence of signs and symptoms analysis is shown in Fig. 3A. The 0–4 years category is shown with more granularity in Fig. 3B.

The prevalence of each manifestation by age at diagnosis was determined, taking into consideration the prevalence at adjacent ages. Fig. 4 represents the modelled prevalence values by age, of all signs and symptoms with the exception of family history of NP-C, allowing definition of characteristic symptomatology at diagnosis of NP-C by age. The modelled prevalence curves for all signs and symptoms observed with a prevalence of >10% in any group in this cohort are shown in Figs. 5–7.

3.3.1. Visceral symptoms

In the pooled cohort, at diagnosis, splenomegaly (historical and/or current) with or without hepatomegaly was the most frequently observed visceral symptom, particularly in infantile, juvenile and young adult patients with NP-C (Figs. 4 and 5). This symptom was observed at a greater prevalence in NP-C cases *versus* controls across all age ranges at diagnosis. Hydrops foetalis, and siblings with foetal ascites were not commonly reported at diagnosis in patients with NP-C, with a prevalence below 10% in all age groups (Fig. 4). The sign siblings with foetal ascites was not reported in controls (data not shown).

3.3.2. Neurological symptoms

VSGP, ataxia and dysphagia became more common with increasing age at diagnosis in NP-C cases, with high prevalence in patients diagnosed with NP-C at >10 years of age (Figs. 4 and 6). With the exception of patients diagnosed at a very young age, VSGP and dysphagia (with or without dysarthria) were much more common in NP-C cases *versus* age-matched controls. Gelastic cataplexy was relatively uncommon at diagnosis in NP-C cases across all age sub-groups; however, this symptom was not observed in any age-matched controls. In NP-C cases, seizures were more commonly observed in adolescence and early adulthood than later in life. Hypotonia, seizures, and delayed developmental milestones were common in children and juvenile patients with NP-C, but prevalence was similar between NP-C cases and age-matched controls across all age ranges at diagnosis. Prevalence of myoclonus was also similar for NP-C cases and controls for all ages. Dystonia and acquired and progressive spasticity were more common at diagnosis in NP-C cases compared with controls in the adolescent and young adult subgroups (Fig. 6).

3.3.3. Psychiatric symptoms

In general, psychiatric disorders were more common at diagnosis in adolescent and adult NP-C cases than in infantile NP-C cases (Figs. 4 and 7). With the exception of patients diagnosed before 4 years of age, for whom prevalence was relatively low, cognitive decline and/or dementia (known as mental regression in infantile patients) was more common in NP-C cases than age-matched controls.

3.3.4. Family history of NP-C

The signs parents or siblings with NP-C, and cousins with NP-C were not observed in controls, being specific to NP-C cases in this cohort (data not shown).

4. Discussion

NP-C is a progressive disease with heterogeneous presentation and variable prognosis depending on disease severity, and age of onset of neurological manifestations [3]. Due to the complexity of symptom presentation, the diagnosis of NP-C presents a great challenge in clinical practice, but timely recognition of symptoms and diagnosis of NP-C is crucial to support the early initiation of symptomatic and disease-specific therapies, and to ensure the best possible outcomes for patients [5].

We assessed the presence of relationships between symptoms from a clinical perspective, and analysed the differences in symptomatology observed in patients at different ages in an international pooled cohort of NP-C case and age-matched controls.

Signs and symptom clusters were closely evaluated in light of clinical experience in patients aged ≤4 years and >4 years. The clusters identified in the current analyses were broadly representative of the various NP-C presentations observed in clinical practice. In patients ≤4 years of age, clinical interpretation suggested that symptoms could be grouped into six sub-clusters: predominantly classical visceral signs, expected in a population of this age; family history of NP-C; ancillary non-specific visceral and neurological signs (two sub-clusters); non-specific signs indicative of onset of neurological symptoms; and more classical neurological symptoms, indicative of disease severity and perhaps reflecting an older age at diagnosis in these particular patients. In patients aged >4 years, clustering appeared to follow a similar, but less detailed picture, with sub-clusters reflecting: non-specific neurological symptoms, perhaps indicative of a younger sub-group of patients; psychiatric symptoms; symptoms that are generally observed in older, more severely affected patients; and general and classical manifestations, widely seen in patients with NP-C > 4 years of age.

Overall, the sub-clusters observed appeared to correlate with observations from clinical practice, with a few exceptions that are to be expected within these populations and with these analyses. In addition to the anticipated influence of patient age and disease severity, the clusters may be influenced by the affected organs. The sub-cluster of psychiatric symptoms observed in patients >4 years of age most likely represents the impact of disease on the central nervous system, seen during the second and third decades of life. Disruption to late neurodevelopment at this age is likely to lead to (treatment-resistant) psychotic symptoms and secondary behavioural disturbances, as a result of the impact of NP-C on global white matter and subcortical grey matter structures [15]. Another of the sub-clusters observed in patients >4 years of age combines symptoms that can, at least partially, be attributed to the characteristic cerebellar pathology of NP-C, with dysarthria and ataxia representing typical cerebellar signs. Furthermore, alterations to muscle tone, cognitive function and saccadic eye movements observed in this patient cohort may result from cerebellar pathology and/or pathologic changes to the basal ganglia associated with NP-C [16]. The clustering of key visceral symptoms was apparent in both age groups, and some symptoms also appeared to be clustered according to

Fig. 2. Cluster analyses of NP-C symptomatology in two populations ≤4 and >4 years of age. Cluster analysis of signs and symptoms of NP-C reported at current age at data collection for NP-C cases and controls. For patients ≤4 years of age, items recorded in the early-onset cohort were analysed. For patients >4 years of age, items used in the original NP-C SI were included in the analysis. (A) Controls ≤4 years of age. (B) NP-C cases ≤4 years of age. (C) Controls >4 years of age. (D) NP-C cases >4 years of age. Clusters and sub-clusters are indicated as rectangular numbered boxes and numbered brackets, respectively. The threshold for clusters $R^2 = 0.2$ in panels (B) and (D) was defined based on the dendrogram and expert opinion; sub-clusters were defined based on expert opinion. n, total number of patients in the sub-group; NP-C, Niemann-Pick disease Type C.
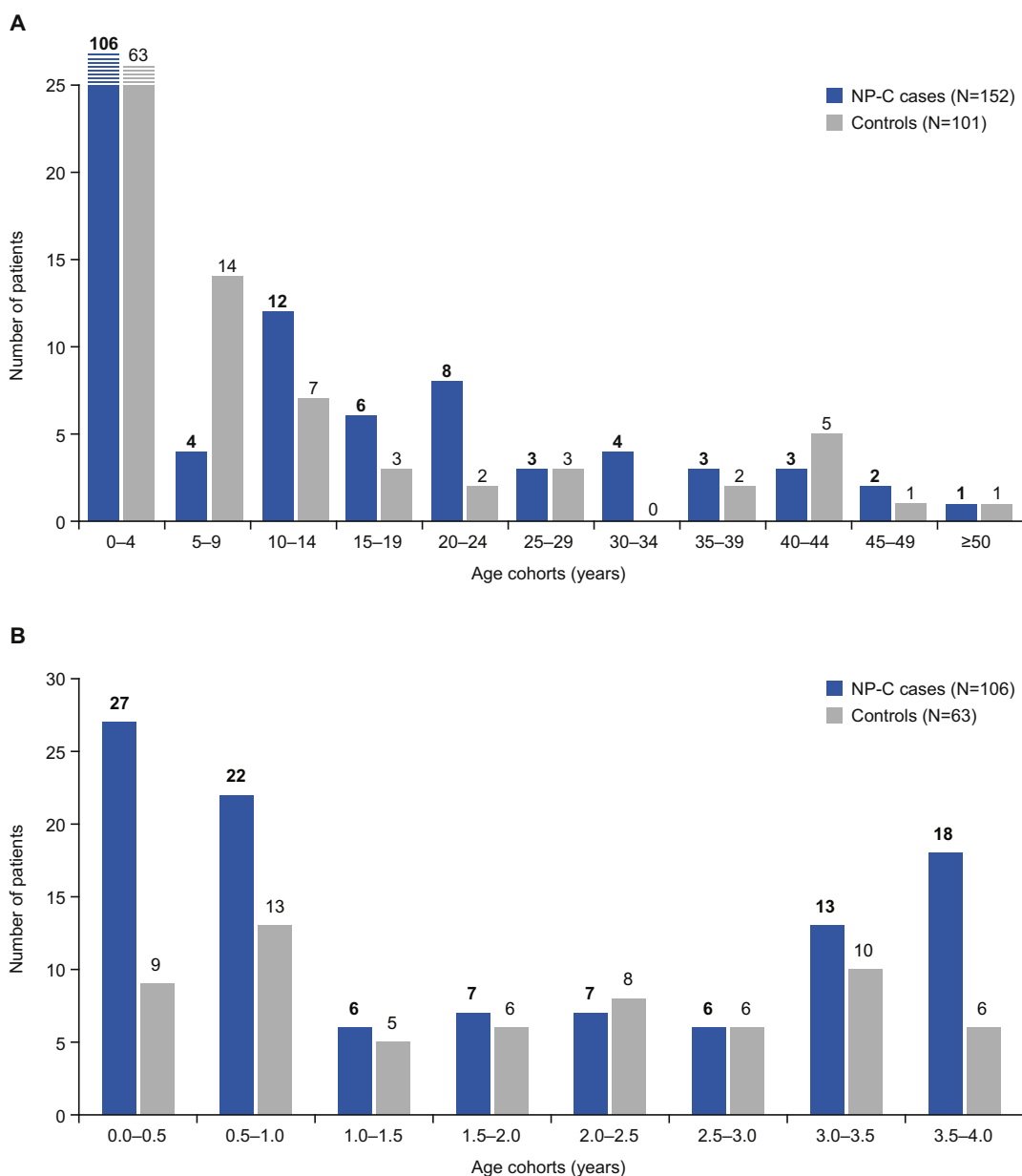
Fig. 3. Distribution of NP-C cases and controls by age at diagnosis. Distribution of NP-C cases and controls by age at diagnosis. (A) Age distribution of NP-C cases and controls in the combined patient cohort. (B) Age distribution of NP-C cases and controls in infantile (0–4 years) patient cohort. Numbers above columns indicate number of patients in each age group. N, total number of patients in the population; NP-C, Niemann-Pick disease Type C.

the localisation of affected regions within organs, for example specific brain regions (cerebellar signs such as ataxia and dysarthria). Other influencing factors may also affect the clustering of signs and symptoms, including the physicians' specialty and triggering of searches for certain symptoms after identification of one.

Analysis of the prevalence of signs and symptoms of NP-C in this cohort showed that key neurological and psychiatric symptoms, VSGP, ataxia, dysphagia and cognitive decline, were commonly observed in NP-C cases diagnosed at >4 years of age. This finding corresponds with observations from clinical practice and current understanding of NP-C symptomatology, and reflects that these symptoms generally occur in patients diagnosed at an older age.

In line with clinical experience, key visceral symptoms such as neonatal jaundice and hepatosplenomegaly were common in patients with NP-C who were diagnosed ≤4 years of age, were more common in NP-C

cases than in controls, and were also clustered together in this age subgroup. This finding supports evidence that these symptoms are frequently found in young patients with NP-C and can be sensitive and specific indicators of the disease [4]. The decreasing prevalence of hepatosplenomegaly in patients with increasing age at diagnosis supports previous findings and observations from clinical practice [3]. It should be noted, however, that lower prevalence of this symptom reported within the older population compared with those diagnosed at a younger age might result from an inaccuracy in reporting, subsequently revealed during retrospective analysis of medical charts, or irregularity in symptom monitoring in older patients.

In agreement with other published data [4], delayed developmental milestones, often presenting as delayed gross or fine motor function in infants and/or delayed language acquisition in young children [3], along with hypotonia and ataxia, were common in infants and young
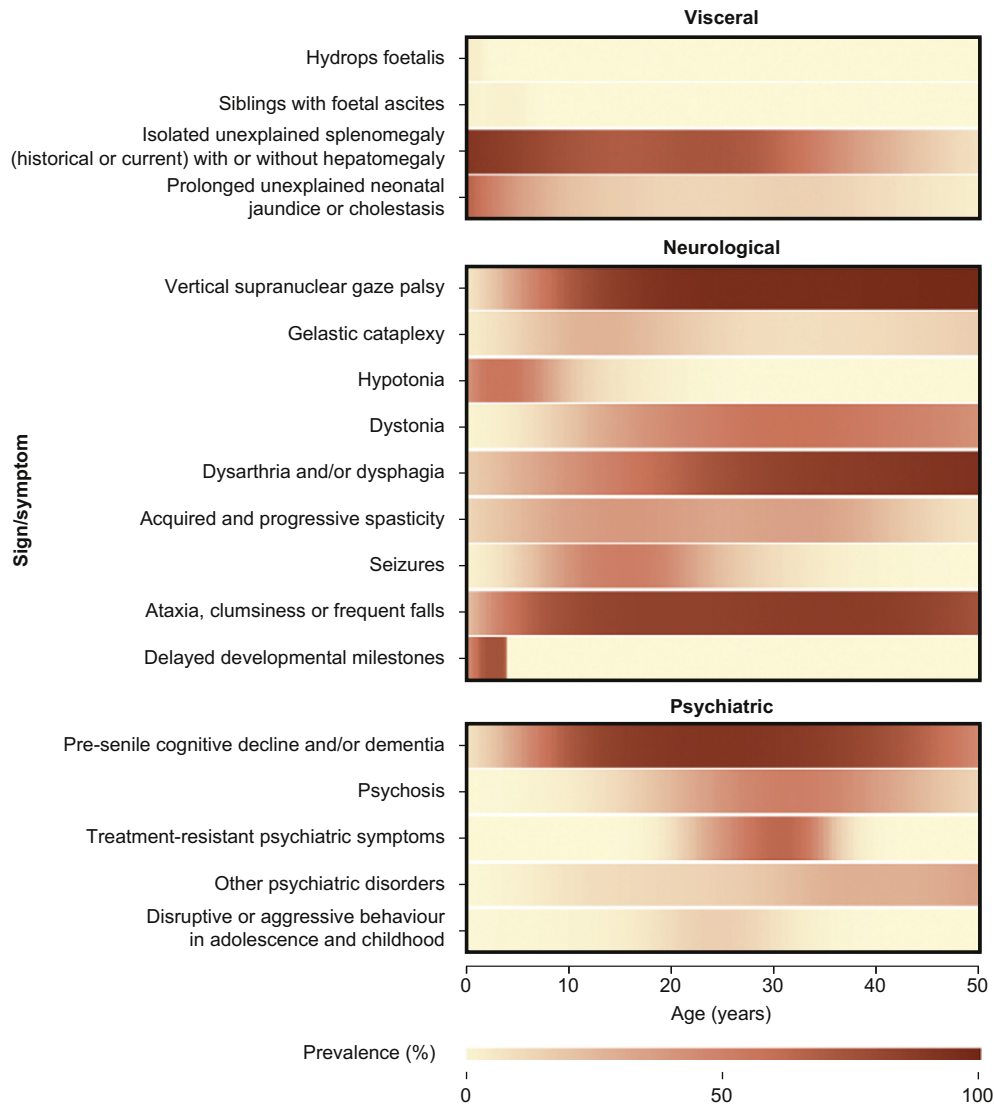
Fig. 4. Prevalence of characteristic symptoms at age of diagnosis in NP-C cases. Prevalence of characteristic symptoms of NP-C at age at diagnosis. Colour gradient across age groups is representative of data from the smoothed prevalence curves. Shading corresponds to different prevalence ranges. NP-C, Niemann-Pick disease Type C.

children in this pooled cohort. These key neurological signs were frequently reported at diagnosis in both NP-C cases and controls, in agreement with previous reports that they are important but non-specific symptoms of NP-C [6].

Despite a relatively low prevalence across all age groups at diagnosis, gelastic cataplexy was not observed in controls at any age, supporting its identification as a highly specific symptom of NP-C [6]. In NP-C cases, seizure prevalence at diagnosis was higher than might be
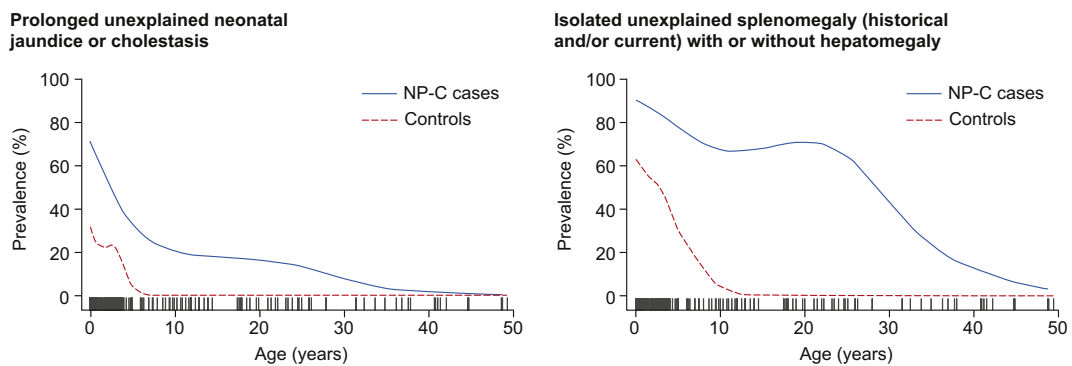
Fig. 5. Prevalence of visceral symptoms at diagnosis in NP-C cases *versus* age-matched controls Individual prevalence curves represent exploratory modelled data obtained at diagnosis for NP-C cases (smooth line) and age-matched controls (dashed line). NP-C, Niemann-Pick disease Type C.
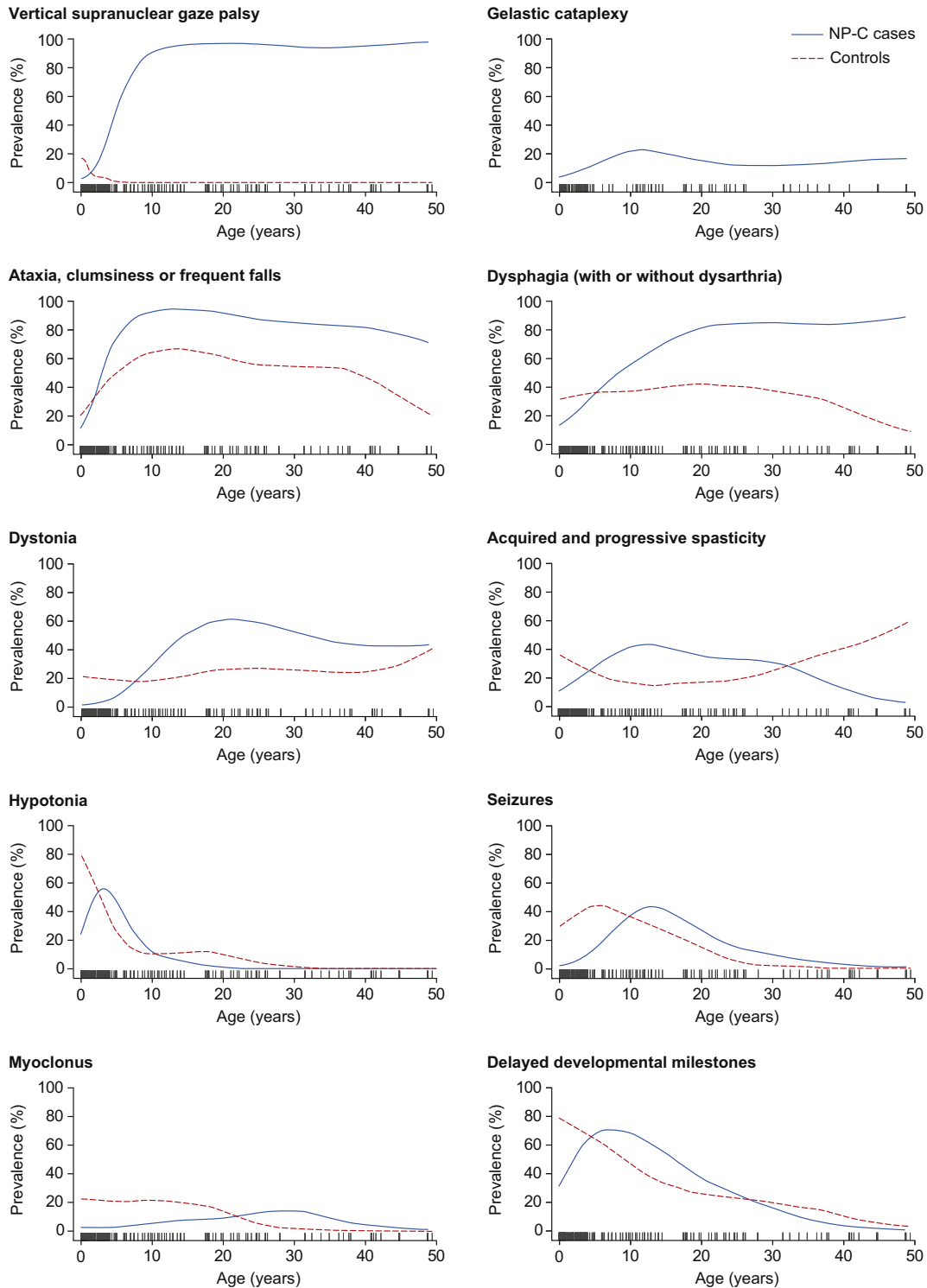
Fig. 6. Prevalence of neurological symptoms at diagnosis in NP-C cases *versus* age-matched controls. Individual prevalence curves represent exploratory modelled data obtained at diagnosis for NP-C cases (smooth line) and age-matched controls (dashed line). NP-C, Niemann-Pick disease Type C.

anticipated from clinical experience in patients diagnosed from 10 to 20 years of age. In general, seizures, despite being a relatively frequent symptom of NP-C, are more commonly noted after a diagnosis of NP-C has been made and may reflect a more severe or advanced disease state [17]. The high prevalence of seizures in this pooled cohort may reflect a more severely affected population. Gelastic cataplexy and seizures were much more common in young patients (<18 years of age),

as might be expected for signs typical of rapidly progressive early-onset disease.

4.1. Limitations of the analyses

These analyses are based on two existing patient cohorts pooled for these analyses, and may not be fully representative of patients
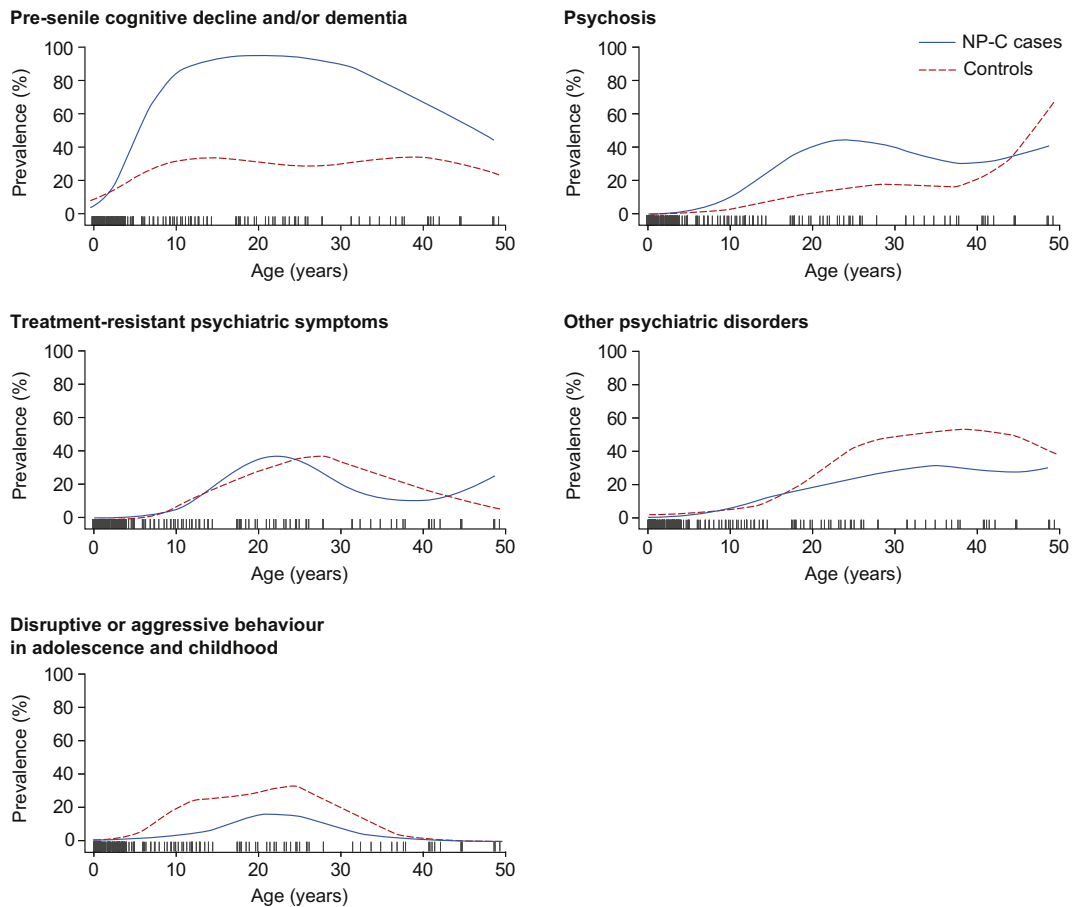
Fig. 7. Prevalence of psychiatric symptoms at diagnosis in NP-C cases *versus* age-matched controls. Individual prevalence curves represent exploratory modelled data obtained at diagnosis for NP-C cases (smooth line) and age-matched controls (dashed line). NP-C, Niemann-Pick disease Type C.

with NP-C as a whole. Low numbers of patients in some age groups constrain the statistical analysis, particularly for the exploratory prevalence analyses. Investigation of symptomatology in larger patient cohorts, and in clinical practice, is required to further understand the symptom manifestations in NP-C.

5. Conclusions

It is anticipated that these data will provide valuable information on the relationship between signs and symptoms of NP-C, and on symptom prevalence at diagnosis, by utilising a diverse and sizable pooled cohort of patients with NP-C. By considering the prevalence of symptoms at diagnosis in patients of different ages, and by highlighting possible correlations between symptoms, physicians can gain valuable insight into NP-C symptomatology. This information may aid the recognition of patients with NP-C within a given age group. These analyses provide a timely and logical review of the characteristic symptomatology of patients diagnosed with NP-C at all ages and contribute to our understanding of the disease, its variable onset and progression.

Abbreviations

NP-C   Niemann-Pick disease Type C
SD   standard deviation
SI   Suspicion Index
VSGP   vertical supranuclear gaze palsy

Declarations

Ethics approval and consent to participate

This retrospective research exclusively involved use of anonymous information. Each contributor determined, according to their local regulations, that ethical committee review was not required for this study.

Availability of data and material

The dataset supporting the conclusions of this article is included within the article and its additional files.

Conflict of interests

EM, MP, CJH, MW and JVT have received consulting fees or honoraria from Actelion Pharmaceuticals Ltd.
SAK is an employee of Actelion Pharmaceuticals Ltd.

Authors' contributions

All authors participated in the drafting of the manuscript, read and approved the final manuscript for submission. JVT carried out statistical analysis and modelling of the data.

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