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RESEARCH REPORT

Screening for Niemann-Pick Type C Disease in a Memory Clinic Cohort

Andreas Traschütz • Michael Thomas Heneka

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Abstract Niemann-Pick type C disease (NPC) is a neurovisceral lysosomal storage disorder with a heterogeneous phenotype including ataxia, cognitive impairment, impairment of vertical saccades, and psychiatric symptoms, among many others. Based on clinical, genetic, and biomarker findings, recent guidelines put forward a screening for atypical and oligosymptomatic forms of NPC in clinical niches with an increased risk. Here, we report methods and results of a negative screening study in the niche of a memory clinic. We retrospectively and prospectively identified 83 patients with unclassified cognitive impairment (15 dementia, 46 mild cognitive impairment, and 22 progressive subjective cognitive decline) before 60 years of age (82 patients between 41 and 60 years). We explored the prevalence of clinical features compatible with NPC and measured plasma levels of chitotriosidase and cholestantriol. The NPC suspicion index indicated high probability for NPC in 3 and moderate probability in 16 patients. Prevalent (>5%) neurological and psychiatric features were depression, seizures, ataxia, dysarthria, and psychotic symptoms. Vertical gaze palsy without parkinsonism was observed in one patient. Cholestantriol levels were only abnormal in one patient. Chitotriosidase levels were susceptible to slight elevations that were reproducible in only two of five patients. Our study does not exclude NPC among memory clinic patients. Instead, we suggest conducting prospective screening studies in younger cohorts that include a focused neurological examination. Excluding minor cognitive impairment and discarding depression as an independent disease symptom probably further improve screening effectivity but may delay or miss therapeutic options in early or mild disease.

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A. Traschütz
Department of Neurology, University Hospital Bonn, Bonn, Germany

M. T. Heneka
Department of Neurodegenerative Diseases and Gerontopsychiatry/Neurology, University Hospital Bonn, Bonn, Germany

M. T. Heneka (✉)
German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
e-mail: michael.heneka@ukb.uni-bonn.de; michael.heneka@ukbonn.de

Introduction

Niemann-Pick disease type C (NPC) is a rare autosomal recessive lysosomal lipid storage disorder caused by mutations in NPC1 (OMIM #257220) or NPC2 (OMIM #607625) in 95% and about 4% of cases, respectively (Patterson et al. 2017). The spectrum of this neurovisceral disease ranges from organomegaly and a developmental delay in infants to a neurodegenerative phenotype with adult onset (Vanier 2010). Among other symptoms, especially ataxia and impaired vertical saccades, the latter includes psychiatric symptoms in more than 40% and progressive cognitive impairment in more than 60% of cases (Sevin et al. 2007). Although none of these symptoms is specific, the assessment of patient history and clinical signs, for example, by means of the NPC suspicion index (NPC-SI), may help to identify clinical patterns suggestive of classical NPC (Wijburg et al. 2012).

Recently, large exome datasets indicated that NPC prevalence could be as high as 1:19,000 because of the frequency of NPC1 gene variants that can cause late-onset disease with oligosymptomatic phenotypes (Wassif et al. 2016).

Therefore, patients with NPC may present without characteristic patterns of symptoms, and probably later than the classical onset before 40 years of age. The detection of these patients has been specifically addressed in updated guidelines (Patterson et al. 2017). Based on progress in the development of biochemical biomarkers and genetic tests, these guidelines recommend a biomarker or genetic screening among patients in clinical niches that may be associated with an increased risk of NPC (Vanier et al. 2016). This has, for example, identified patients with NPC in a cohort with unexplained ataxia (Schicks et al. 2013).

In the present study, we hypothesized that NPC may be more common than expected in the niche of patients with young onset dementia, which is remarkably prevalent (50–60:100,000) and diagnostically challenging (Rossor et al. 2010). We prospectively and retrospectively screened patients up to 60 years of age that presented to an academic memory clinic with variable degrees of unexplained cognitive decline. Although no patient was identified, we share our experience including the prevalence of symptoms of the NPC spectrum and the results of biomarker measurements in such a cohort. Importantly, we discuss optimized screening strategies that will probably facilitate the detection of NPC in this clinical niche in future studies.

Methods

From a local registry with 1,811 patients that presented to the memory clinic of the University Hospital of Bonn, Germany, between January 2011 and December 2015, we retrospectively identified 350 patients up to 60 years of age without classified diagnosis. With approval of the local ethics committee (279/10), these patients were contacted with a letter that informed about rare metabolic causes of cognitive impairment and offered further information and diagnostic work-up upon request. Via telephone interview with 144 patients (41%) that responded, a physician obtained a detailed history, family history, and necessary information to determine the NPC-SI in conjunction with data and a neurological examination extracted from the patient record (Wijburg et al. 2012). Testing for plasma chitotriosidase and cholestantriol (cholestane-3β,5α,6β-triol, gas chromatography-mass spectrometry method) levels was performed when NPC was considered possible based on clinical grounds (Reunert et al. 2015). This included 45 patients with dementia or mild cognitive impairment of unknown cause, mild cognitive impairment with concomitant depression (refractory to treatment or without apparent extrinsic factors), and progressive subjective cognitive decline. All degrees of memory complaint were rated as regression, i.e., presenile cognitive decline in the NPC-SI. Based on the same criteria, we prospectively identified and tested 38 patients with possible NPC between January and July 2016. All patients with mild cognitive impairment or dementia had at least routine blood tests (including blood count, creatinine, liver enzymes, folic acid, vitamin B12, and thyroid stimulating hormone), neuropsychological screening tests (Mini-Mental State Examination (MMSE) or others), and brain imaging. Genetic testing for NPC was performed in patients with elevated biomarker levels in two consecutive samples.

Results

A diagnosis of NPC was considered in 83 patients (36 male), including 45 and 38 patients in the retrospective and prospective group, respectively. The mean age of the cohort was 53.3 years; all except one patient (27 years) was 41 years or older. Twenty-two patients (27%) had subjective cognitive decline, 46 (55%) had mild cognitive impairment, and 15 patients (18%) were diagnosed with dementia of unknown cause. Data of MMSE was available in 75 patients (90%) and was, on average, 29.1, 26.0, and 19.7, respectively.

Beside cognitive impairment, we observed both neurological and psychiatric features of the NPC phenotype. Of note, 39 patients (47%) had at least mild depression. Other psychiatric diagnoses were psychosis (hallucinations or delusions), adult attention deficit hyperactivity disorder (ADHD), anxiety disorder, and bipolar disorder (Table 1). Neurological signs or symptoms were seizures, ataxia, dysarthria, and myoclonus. One case each was identified with vertical gaze palsy (without parkinsonism), dystonia, or spasticity.

Table 2 provides a summary of patients with either positive plasma biomarkers or at least moderate disease probability according to the NPC-SI. With a range between 20 and 80, the NPC-SI indicated low, moderate, and high probability (<40, 40–69, ≥ 70) in 64, 16, and 3 patients, respectively, when all degrees of cognitive impairment were rated as presenile cognitive decline. Regarding biomarkers, levels of cholestantriol were elevated in two consecutive measurements in one patient with a high-probability NPC-SI. Levels of chitotriosidase were elevated in five patients but confirmed in a second measurement in only two patients with an NPC-SI indicating low probability. Genetic testing for NPC was performed, but negative for both alleles in all three patients with elevated biomarker levels. Based on our cohort of 83 patients, the 95% confidence interval of the prevalence estimate for NPC was 0–4.4/100 patients (Wilson interval).

Clinical follow-up of more than 12 months was available in only two of five patients with high-probability NPC-SI and/or elevated plasma biomarkers. Chronic valproate intoxication was diagnosed in the patient with negative biomarkers, but the highest NPC-SI. In one patient

Table 1 Prevalence of features related to the NPC phenotype

Clinical feature	*N* (%)
Depression	39 (47)
Seizures	6 (7)
Ataxia	5 (6)
Dysarthria	4 (5)
Psychosis	4 (5)
Adult ADHD	4 (5)
Anxiety	3 (4)
Myoclonus	2 (2)
Vertical gaze palsy	1 (1)
Bipolar disorder	1 (1)
Dystonia	1 (1)
Spasticity	1 (1)

ADHD attention deficit hyperactivity disorder

Table 2 Summary of patients with at least intermediate risk NPC-SI or elevated biomarkers

Age	Sex	COG	MMSE	NPC-SI	CHO	CHI	Additional clinical features
41	M	MCI	n.a.	81	–	–	Seizures, vertical gaze palsy
60	M	DEM	28	80	–	–	Vertical gaze palsy without parkinsonism
60	F	MCI	26	80	+	–	Ataxia, dysarthria
60	M	MCI	29	67	–	(+)	Ataxia, depression, developmental delay, psychosis
44	F	SCD	30	65	–	(+)	Ataxia, depression, anxiety
54	M	DEM	26	65	–	–	Ataxia, dysarthria, depression
42	F	MCI	n.a.	57	–	–	Ataxia, depression, developmental delay
57	M	MCI	28	55	–	–	Ataxia, depressions
43	F	MCI	n.a.	55	–	–	Spasticity, depression
57	F	DEM	n.a.	51	–	–	Dysarthria, myoclonus
58	M	DEM	14	51	–	–	Ataxia, seizures
49	F	SCD	29	50	–	–	Dystonia, depression
54	M	SCD	29	50	–	–	Dysarthria, depression
49	F	MCI	27	50	–	–	Dysarthria, depression
48	F	DEM	19	47	–	–	Developmental delay, seizures, depression
56	F	SCD	27	46	–	–	Seizures, depression
59	M	MCI	29	46	–	–	Seizures, bipolar disorder
54	M	MCI	29	46	–	–	Seizures, depression
57	F	DEM	n.a.	41	–	–	Myoclonus
57	M	MCI	29	25	–	+	Depression
60	M	MCI	26	20	–	+	
55	M	MCI	21	20	–	(+)	

CHI chitotriosidase, *CHO* cholestantriol, *DEM* dementia, *MCI* mild cognitive impairment, *n.a.* not available, *NPC-SI* Niemann-Pick type C suspicion index, *SCD* subjective cognitive decline, (+) negative in second sample

with elevated chitotriosidase, but low-probability NPC-SI, cognitive impairment was related to severe depression he developed over the course of 3 years.

Discussion

Following recommendations by recent guidelines, the present study screened for NPC in the clinical niche of patients with unclassified cognitive impairment. Although our screening was negative, several aspects are important and may inform future studies.

As a major finding, our study provides estimates of clinical features in memory clinic cohorts that are part of the NPC spectrum and assessed upon risk stratification by the NPC-SI (Wijburg et al. 2012). In general, the prevalence of about 15% of patients with unclassified or uncertain diagnosis is consistent with previous data (Hejl et al. 2002). This indicates that our study population is probably representative of other memory clinic settings. A comparable 40% prevalence of depression has also been observed by others (Knapskog et al. 2014). To our knowledge, there are no specific estimates for ataxia or dysarthria in memory clinics. Of note, their presence in 5% of our patients was found based on nontargeted neurological examinations by both neurologists and psychiatrists. Therefore, their actual prevalence may be higher. Nontargeted neurological examinations could also be the reason for the low frequency of vertical supranuclear gaze palsy, which requires assessment of both smooth-pursuit eye movements and saccades, not only in NPC (Salsano et al. 2012). Although this may be the correct estimate in patients below 60 years of age, we expected a higher prevalence because of definite impairment of vertical, especially downward gaze in patients above that age (Oguro et al. 2004). Importantly, the current study shows that because of the presence of all of these features, the NPC-SI may indicate high probability of NPC in about 4%, and at least moderate probability in more than 20% of patients in memory clinics. This rate of false positives will probably be lower in an updated version of the NPC-SI (Hendriksz et al. 2015). This version only puts special weight on combinations of more specific neurological and psychiatric symptoms, specifically presenile cognitive decline, psychotic symptoms, vertical supranuclear gaze palsy, and gelastic cataplexy.

Regarding biomarkers, the present study cannot draw any conclusion about sensitivity, but it provides data on the specificity of chitotriosidase and cholestantriol in a memory clinic cohort. Although chitotriosidase is a widely applied biomarker for lysosomal storage disorders, levels can be elevated in common disorders such as diabetes mellitus (Żurawska-Płaksej et al. 2016) and, importantly, increase with age (Bouzas et al. 2003). This is probably the reason why five patients in this study had at least one measurement with elevated plasma levels. Because levels may also be normal in NPC with late onset (Vanier et al. 2016), we conclude that chitotriosidase may be a suboptimal biomarker for a screening in aged memory clinic cohorts. Levels of cholestantriol were recently shown to be independent of age and 98% specific for NPC in a large sample of 1,902 patients (Reunert et al. 2016). With only one false-positive patient, this is in consistency with the specificity observed in our study and makes cholestantriol a promising biochemical marker to screen for late-onset NPC. Nevertheless, the present study also shows that biomarkers (and clinical features) with limited sensitivity and specificity yield more than 1% false positives when screening populations with low prior disease probabilities (Geberhiwot et al. 2018). Although cholestantriol levels can be elevated in 25% of heterozygous carriers (Jiang et al. 2011; Reunert et al. 2016), this was not observed in the present study. Inversely, because levels in 75% of carriers are normal, we cannot exclude NPC1 or NPC2 heterozygotes among those in our cohort not genetically screened. Such NPC1 and NPC2 heterozygosity has recently been found in 4 out of 50 patients with a dementia plus syndrome (Cupidi et al. 2017).

The negative outcome of this study possibly indicates that NPC is not found in late-adult patients with cognitive impairment unless there are clinically predominant other features of NPC (Patterson et al. 2013). However, our results do not support the definitive conclusion that patients with NPC do not present to memory clinics. Statistically, the upper limit of our prevalence estimate suggests that the study cohort may just have been too small. Beyond that, the sensitivity of cholestantriol levels for NPC is only about 92–97% (Jiang et al. 2011; Reunert et al. 2016). Although unlikely, direct genetic testing of the entire study cohort could thus have identified NPC cases. Nevertheless, the negative screening raises the question whether its inclusion criteria have been adequate. Because of reported onsets of neurological symptoms as late as 56 years of age, the present study included patients up to 60 years of age (Vanier 2010). Due to referral practice, almost all patients were in fact older than 40 years of age. For comparison, recent guidelines specify at-risk groups with onsets before 40 years of age (Patterson et al. 2017). We therefore suggest that future screening studies should first target memory clinics with younger patients. A second important factor was probably the inclusion of patients with quantitatively and qualitatively different cognitive impairment. The present study not only included patients with dementia but also with mild cognitive impairment and subjective cognitive decline because potentially reversible causes of cognitive impairment, including metabolic diseases, are more prevalent in the latter two categories than in the

dementia stage (Hejl et al. 2002). Moreover, patients with manifest NPC may have MMSE results in the range of mild cognitive impairment (Bauer et al. 2013). However, the inclusion of patients with minor degrees of memory impairment may as well have lowered the prior probability for a severe organic disease. Qualitatively, we included patients with any pattern of cognitive impairment in neuropsychological assessments or with abnormal screening tests alone and excluded patients with a classified diagnosis. According to recent guidelines, however, it might also be reasonable to actively screen for NPC in patients with a specific pattern of executive problems and deficits of working memory and verbal fluency suggestive of frontotemporal dementia, especially in conjunction with behavioral alterations (Klarner et al. 2007; Patterson et al. 2017). Finally, the present study included patients with depression, which can be either an independent symptom of NPC (or other neurodegenerative diseases), but also the primary cause of cognitive impairment, especially in younger patients (Patterson et al. 2012; Richard et al. 2013). Because of the prevalence of the latter, and consistent with the updated NPC-SI, future screening efforts should probably not prioritize patients with cognitive impairment and depression unless additional symptoms of NPC are present.

In conclusion, the present study cannot exclude the presence of NPC in the clinical niche of memory clinic patients. We suggest conducting prospective screening studies in younger and larger cohorts that include a focused neurological examination and measurements of plasma cholestantriol as a biomarker. Excluding minor cognitive impairment and discarding depression as an independent disease symptom probably further improve screening effectivity but may delay or miss therapeutic options in early or mild disease.

Synopsis

Niemann-Pick type C disease was not detected among memory clinic patients despite cases with abnormal suspicion index or plasma biomarkers, but future screenings may be positive in larger and younger cohorts with disease characteristics in addition to cognitive impairment and depression.

Compliance with Ethics Guidelines

Conflicts of Interest

A.T. has received travel fees by Actelion Pharmaceuticals.

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Informed Consent

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Author Contributions

Andreas Traschütz acquired the data, performed the analysis, and wrote the manuscript.

Michael T. Heneka planned the study and wrote the manuscript.

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