# The hidden Niemann-Pick type C patient: clinical niches for a rare inherited metabolic disease

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## Abstract

*Background:* Niemann-Pick disease type C (NP-C) is a rare, inherited neurodegenerative disease of impaired intracellular lipid trafficking. Clinical symptoms are highly heterogeneous, including neurological, visceral and/or psychiatric manifestations. The incidence of NP-C is underestimated due to under-recognition and/or misdiagnosis across a wide range of medical fields. New screening and diagnostic methods provide an opportunity to improve detection of unrecognized cases in clinical subpopulations associated with a higher risk of NP-C. Patients in these at-risk groups ('clinical niches') have symptoms that are potentially related to NP-C, but go unrecognized due to other, more prevalent clinical features and lack of awareness regarding underlying metabolic causes.

*Methods:* Twelve potential clinical niches identified by clinical experts were evaluated based on a comprehensive, non-systematic review of literature published to date. Relevant publications were identified by targeted literature searches of EMBASE and PubMed using key search terms specific to each niche. Articles published in English or other European languages up to 2016 were included.

*Findings:* Several niches were found to be relevant based on available data: movement disorders (early-onset ataxia and dystonia), organic psychosis, early-onset cholestasis/(hepato)splenomegaly, cases with relevant antenatal findings or fetal abnormalities, and patients affected by family history, consanguinity and endogamy. Potentially relevant niches requiring further supportive data included: early-onset cognitive decline, frontotemporal dementia, parkinsonism, and chronic inflammatory CNS disease. There was relatively weak evidence to suggest amyotrophic lateral sclerosis or progressive supranuclear gaze palsy as potential niches.

*Conclusions:* Several clinical niches have been identified that harbor patients at increased risk of NP-C.

**Key words:**

Niemann-Pick disease type C (NP-C); diagnosis; screening; clinical niche; differential diagnosis; epidemiology; inborn errors of metabolism (IEM)

**Short title:**

*Clinical niches for NP-C*

## Introduction

Niemann-Pick disease type C (NP-C) is a rare, autosomal recessive, neurodegenerative disease caused by mutations in the *NPC1* or *NPC2* gene that lead to impaired intracellular lipid trafficking and excess storage of glycosphingolipids in the brain, liver and other tissues [1, 2, 3, 4]. The disease shows a sporadic, panethnic occurrence, affecting between 1:89,000 and 1:100,000 individuals [5, 6, 7, 8, 9].

NP-C can be regarded as a role model for other ultra-rare, inherited neurodegenerative diseases in a number of ways. Its true incidence is likely underestimated due to under-recognition and misdiagnosis. Patients with NP-C show extreme clinical heterogeneity in their symptom profiles, ages at disease onset, and rates of disease progression [10]. Presenting symptoms are often mild and non-specific. Multiple referrals are often required between primary care and a wide range of medical specialties including, but not limited to, pediatrics, adult neurology, hepatology, hematology and psychiatry. The diagnosis of NP-C therefore requires multidisciplinary clinical work-up and, ultimately referral to specialist centers with

expertise in diagnostic laboratory tests [10, 11]. As a result, many patients experience significant delays to diagnosis [7, 8, 12, 13].

The core neurological manifestations of NP-C affect movement (e.g., cerebellar ataxia), manipulation (e.g., dystonia, dysmetria), speech (dysarthria), and swallowing (dysphagia) [11, 14]. Vertical supranuclear gaze palsy (VSGP) is considered highly characteristic, and seizures and gelastic cataplexy are also often reported [10, 15]. Visceral symptoms include prolonged neonatal jaundice, hepatosplenomegaly and other cholestatic symptoms [10, 16, 17]. A range of psychiatric and behavioral disorders such as psychosis, bipolar disorder, developmental delay, and difficulties at school are frequently observed [10, 18, 19].

Certain clinical subpopulations are associated with a higher risk of NP-C compared with the general population. These 'clinical niches' comprise patients with symptoms that are potentially related to NP-C, but which go unrecognized due to other, more prevalent clinical features or a lack of emphasis and awareness regarding rare underlying metabolic causes (e.g., with complex neurological areas or in psychiatric practice). Targeted screening in cohorts of ‘at risk’ patients from such clinical niches may reveal previously unrecognized cases of NP-C. Fortunately, improved genetic analysis methods (e.g., next-generation sequencing [NGS] and gene panel testing) [9, 20, 21, 22, 23, 24], disease biomarkers (e.g., oxysterols, lysosphingolipids and bile acids) [25, 26, 27, 28, 29, 30], and clinical screening tools (the NP-C suspicion index [NPC-SI]) [7, 21, 31, 32, 33] are increasingly becoming available [21] and provide the opportunity to improve the detection of previously hidden cases of NP-C.

Expert consensus based on published evidence has identified the following potential clinical niches for NP-C: movement disorders (early-onset ataxia [EOA] and dystonia); early-onset cognitive decline (EOCD); frontotemporal dementia (FTD); parkinsonism; progressive

supranuclear gaze palsy (PSP); organic psychosis; amyotrophic lateral sclerosis (ALS); unclear neuroinflammatory diseases; and hepatosplenomegaly and/or early-onset cholestasis. A family history of NP-C, and patients with antenatal findings or fetal abnormalities related to the disease also represent potential niches.

The following report provides a comprehensive review of all up-to-date information on known and putative clinical niches for NP-C. We aim to highlight clinical niches where future screening is considered likely to reveal new cases where it might previously have been overlooked.

## Methods and results

This non-systematic review of the literature was designed to provide an educational overview of current evidence regarding the occurrence of NP-C within 12 potential clinical niches and symptoms/methods that can be employed to aid in the identification of NP-C. This review was conducted according to a two-step process: (1) identification of potential clinical niches by simultaneous expert appraisal of medical fields in which new NP-C cases most often present, and specific diseases or disease areas within each relevant medical field that are most commonly associated with NP-C; and (2) assessment of identified niches based on comprehensive assessment of available, relevant evidence and expert opinion, including findings from clinical examination, biomarker evaluations, and genetic mutation analyses as well as other diagnostic clues (e.g. cranial imaging assessments) observed in NP-C.

Data were identified by targeted literature searches of EMBASE and PubMed using key search terms specific to each niche. Articles published in English or other European languages up to 2016 were included. Priority was given to more recent articles.

Publication types considered suitable for inclusion included systematic reviews and meta-analyses, randomized controlled trials, epidemiological studies (case–control studies, cohort studies) and highly relevant narrative reviews. Given the rare nature of NP-C, case reports were also included. Once identified as relevant, all articles were screened for inclusion by in-depth appraisal of data and other content. References from each included article were also assessed for inclusion.

The relevance of each clinical niche to NP-C was finally appraised, and classified as "highly relevant", "potentially relevant", or "not relevant" for NP-C based on the frequency of diagnosed patients in published reports, expert clinical experience, and other supporting information.

***Familial aspects and ancestry***

A family history of NP-C and births from consanguineous parental relationships are widely acknowledged as powerful factors in predicting and detecting new cases of NP-C [10, 178, 179, 180, 181, 182]. In NP-C cohorts from the UK, Europe and Australia, 22–38% of cases were related [6, 7, 32]. However, the high proportion of NP-C patients with compound heterozygote genotypes makes the study of genotype–phenotype correlations challenging [183, 184, 185]. NP-C symptoms can vary widely among family members, even in those with identical genetic mutations. Family studies in the UK and Czech Republic NP-C cohorts identified clinically asymptomatic siblings of patients with both early- and late-onset NP-C [6, 56].

Regions where consanguineous relationships are common (up to 34% of marriages in some regions) tend to be associated with a higher prevalence of autosomal recessive disorders,

including NP-C [179, 180, 181, 186, 187, 188, 189, 190, 191, 192]. While no published studies have directly addressed the influence of endogamy on the occurrence of NP-C, 4/24 patients (17%) diagnosed with NP-C were from consanguineous parents in a series of patients evaluated in Spain (Pocovi M, personal communication).

NP-C is a pan-ethnic disease, so endogamy is not considered such a relevant epidemiological influence on its occurrence. However, some mutations do tend to be localized to specific regions [184, 193]. Regional genetic NP-C isolates are reported from the Greek Islands and Nova Scotia [194, 195]. The incidence of NP-C in the endogamous population of Yarmouth County in Nova Scotia was approximately 1% [196].

Sequencing methods for *NPC1/NPC2* variants are expected to contribute valuable data on the influence of consanguinity and endogamy on NP-C and carrier genotypes in the future [9]. Whole-exome sequencing in 143 multiplex consanguineous families associated with autosomal-recessive neurogenesis disorders detected previously reported homozygous *NPC2* mutations in a male index case (i.e., the first patient diagnosed within his family) as well as his sibling [197]. This was an intriguing finding as neither of these cases displayed progressive neurodegeneration or hepatosplenomegaly typical for their genotype, making it unlikely that they would have been detected based on clinical screening methods. To a degree, this finding casts some doubt on the variant classification applied. Targeted screening based on direct gene sequencing in 510 patients from the Turkish NP-C cohort identified two new patients with NP-C among family members of four index cases, and revealed an overall heterozygous *NPC1*/*NPC2* mutation frequency of 22.7% (Topçu, personal communication).

Substantial published data show that family history is the strongest indicator for possible NP-C cases, even among asymptomatic siblings. Parental genetic studies should be conducted in all index cases and their family members in order to confirm homozygous status and identify/track heterozygote carriers [6, 7, 8, 10].

Genetic analyses, direct gene sequencing, and close monitoring are strongly recommended in siblings of patients with confirmed NP-C in order to identify further, as-yet undetected cases [8,10,11,55].

Biomarker screening, if available, could offer rapid diagnostic information in endogamous populations. In addition, if a particular region has a system in place to screen for rare metabolic diseases, it would be useful to include common *NPC1* variants in the relevant gene panel in order to detect new cases and provide genetic counseling.

***Movement disorders – early-onset ataxia (EOA)***

Cerebellar ataxia is estimated to occur in 85–90% of NP-C patients, but in isolation it is not a specific clinical sign of the disease [7, 8, 10, 13, 34]. NP-C is not common among patients with pure cerebellar ataxia, or in patients with spastic presentations, and can be discounted in congenital, non-progressive ataxia [13, 34, 35, 36]. Patients with NP-C fall into the diagnostic category of 'early-onset ataxia' (EOA) due to ataxia onset below 40 years of age [13, 31, 34, 37, 38, 39, 40]. Although frequent, EOA may be absent in the initial stages of the disease.

In NP-C, EOA typically presents as a 'slow ataxia' that is frequently combined with dystonia, and in some patients, myoclonus [5, 36, 41]. Gait itself may appear normal at early stages, but

movements may be slowed and tandem gait may be well performed, despite many years of disease progression [5].

Clinical diagnostic algorithms may aid in differential diagnosis, particularly among patients with unexplained ataxia [31, 38, 42, 43, 44, 45]. Symptoms that are observed more frequently alongside ataxia in patients with NP-C compared with the general EOA population, which can thus serve as highly specific signs include: 1) cognitive decline/psychiatric disturbances; 2) VSGP; and 3) dystonia (specifically in the hands). A study in 133 EOA patients reported a 'two out of three rule' that reliably identified patients with unexplained EOA [31]. This simple screening method is based on the co-occurrence of EOA with at least two of the three specific concomitant NP-C symptoms mentioned above, and provides sensitivity and specificity for NP-C (90% in both cases).

A clinical screening study in 24 patients with cerebellar ataxia and pre-senile cognitive decline identified four NP-C cases (17% incidence) [34]. Genetic screening methods have been shown able to detect and diagnose NP-C among EOA patients in whom it might otherwise be missed during differential diagnosis [34, 46]. A high-throughput gene sequencing study using an ataxia gene panel in 204 patients with EOA confirmed diagnosis of NP-C in six patients – a 2.9% incidence [20]. The total frequency of *NPC1* gene variants was 8/192 (4.17%), representing significant enrichment compared with a frequency of 1.6% in the control cohort ($p = 0.011$) [20].

Overall, published evidence showing a raised frequency of NP-C in the clinical EOA population indicates that unexplained EOA is a highly relevant clinical niche for the detection of new NP-C cases [20, 31, 56].

***Movement disorders - dystonia***

Dystonia represents the third most common movement disorder and is acknowledged as one of the core neurological manifestations of NP-C, occurring in 40–50% of diagnosed cases [13, 37, 41, 47]. In affected patients, dystonia contributes strongly to patient disability [14]. It can either be focal, affecting the hands, face or upper limbs, or more generalized, affecting gait [10, 47]. Dystonia tends to occur later than other neurological signs during the course of NP-C, and has been reported most frequently in the juvenile and adolescent/adult neurological onset forms [8, 10, 13, 37].

The neuropathological changes underlying dystonia are complex. Dystonia is related to basal ganglia dysfunction, and correlates with pathology in the striatum [10, 39, 47]. Along with other genetic causes, dystonia associated with NP-C may also be related to cerebellar dysfunction [48, 49].

Over 42 hereditary disorders with associated neurodegeneration have dystonic symptoms, which can be categorized into two groups: monogenetic forms with assigned genetic loci (primary dystonias) and complex dystonia (‘dystonia plus') syndromes [50]. 'Dystonia plus' syndromes, which include NP-C, Wilson’s disease, GLUT-1 deficiency and organic acidurias, comprise dystonia along with concomitant neurological and systemic features [50, 51].

Patients with dystonia plus syndrome, especially those displaying progressive dystonic signs and one or more of ataxia, myoclonus, VSGP, dysarthria, dysphagia, cognitive decline, psychiatric manifestations, cataplexy and/or splenomegaly, have an increased likelihood of NP-C [32, 38, 39, 41, 52]. Ataxia is a particularly common concomitant neurological sign [5, 31]. A young age at onset (<40 years of age) can help distinguish dystonia related to NP-C

from that associated with middle-age cervical torticollis. Focal dystonic features typically seen in NP-C include hand dystonia with wrist flexion and a forced (subtle) smile during speech due to dystonia of the jaw muscles (Iodice R, personal communication). Other visible symptoms such as facial grimacing and 'round the houses' sign (i.e., corrective horizontal saccades to accomplish upward voluntary pursuit movements) have also been described [53].

Based on observations from patients visiting specialist/tertiary referral clinics, it is estimated that up to 2% of dystonia patients could be diagnosed with NP-C, possibly even more [54]. While a 'genetics first' approach is sometimes recommended for diagnosis in cases of unexplained dystonia, initial biomarker-based methods can provide more rapid findings where underlying inherited metabolic diseases are suspected.

Dystonia is a commonly encountered yet complex neurological sign in clinical practice. Based on evidence to date, it is considered essential to increase awareness of NP-C as a possible underlying cause. The clinical dystonia population should be considered as a relevant clinical niche for further targeted screening for NP-C. However, the complexity of differential diagnosis related to dystonia requires that patient cohorts be clearly defined.

***Early-onset cognitive decline (EOCD)***

Pre-senile dementia or EOCD presents before the age of 65 years, and is being recognized more frequently [29]. Most cases of EOCD are related to Alzheimer's disease (AD), but inherited neurodegenerative etiologies, including NP-C, are being reported more frequently as the underlying causes [29, 55, 56].

NP-C shares a number of neuropathological features with AD and other dementias such as FTD and Lewy body dementia. Published data indicate a potential link between *NPC1/NPC2* mutations and 'dementia plus' syndromes (i.e., where cognitive impairment is accompanied by other neuropsychiatric and systemic symptoms) [57]. Amyloid beta deposition, neurofibrillary tangles (NFTs), and tau-related pathology are all frequently seen in NP-C [58, 59, 60], although it is not known whether these features are intrinsically linked with lysosomal trafficking defects, or represent more non-specific signs of neurodegeneration in NP-C [61, 62, 63, 64]. Further, published data suggest a possible connection with apolipoprotein E4 (Apo E4), the principal cholesterol trafficking apolipoprotein in the brain, and a known risk factor associated with AD [65, 66].

EOCD is observed during disease progression in almost all patients with adolescent/adult-onset NP-C [47, 67, 68]. EOCD in adult-onset NP-C often presents with concomitant psychiatric signs [7, 10, 19, 35, 47, 52, 67, 69, 70, 71]. As a result, NP-C is sometimes misdiagnosed as endogenous psychiatric disease, in particular schizophrenia [72]. EOCD is less commonly recognized among patients with childhood-onset NP-C, although intellectual developmental disorder, poor school performance and learning disabilities are often reported in affected children [7, 8, 13, 30, 35, 73].

Patients presenting with EOCD should be assessed for all cognitive domains, behavioral features, psychiatric history, and functional impairment [56]. Adults with NP-C may have a specific profile of cognitive deficits [68]: early signs of cognitive impairment in NP-C comprise reduced executive function, processing speed and verbal memory due to frontal-subcortical deficits [47, 68]. As the disease progresses, further general cognitive decline and gradual loss of abilities to perform daily tasks occur alongside prominent memory and

behavioral impairments [10, 73, 74, 75]. Appropriate neuropsychological tests with elements of staging to disease severity may help to detect NP-C [68]. Trail Making tests A & B and verbal fluency tests may prove useful in patients with mild disease. The Mini-Mental Status Examination [MMSE], Corsi Block-tapping, Find Similarities, and Clock Drawing Tests are appropriate for those with more advanced disease.

There are only a few published NP-C screening studies among patients with EOCD. Data indicate that concomitant neurological symptoms can help to detect new cases. One genetic screening study indicated possible enrichment for NP-C among 250 patients with 'pre-senile cognitive decline' (i.e., EOCD) with and without psychiatric symptoms [54]. Another study in 24 patients with EOCD and degenerative ataxia identified four cases of NP-C (17% incidence), which increased to 31% among patients who additionally showed VSGP [34]. The NPC-SI takes cognitive impairment into account, and could represent an effective screening method for NP-C in EOCD [32, 33, 76].

Despite the paucity of data from published screening studies, the clinical EOCD population is considered a relevant clinical niche for NP-C. Specific neuropsychological tests as well as the NPC-SI are considered applicable for screening among EOCD patients.

***Frontotemporal dementia (FTD)***

FTD is a leading cause of dementia in patients aged <65 years [77, 78], and shares a number of features in common with NP-C at the genetic, clinical and neuropathological levels, particularly among adult-onset cases. The behavioral variant of FTD is characterized by behavioral and/or cognitive deficits manifesting as early and progressive changes in personality (e.g., impulsivity, poor judgement), impaired language ability, and loss of

organizational skills [77, 79, 80]. Patients with NP-C also often show a history of developmental problems and EOCD, and prominent executive dysfunction is frequently observed, particularly among patients with later-onset disease [7, 8, 10].

Psychotic symptoms are often reported in both FTD and NP-C [7, 19, 81, 82, 83, 84, 85, 86], and are associated with disrupted frontotemporal pathways and impaired frontal-subcortical connectivity [72, 87]. As in NP-C [47, 72, 81, 82, 88], psychosis in adults with FTD frequently leads to misdiagnosis with schizophrenia, schizoaffective disorder or bipolar disorder, often many years before a final diagnosis is confirmed [85, 89, 90, 91, 92].

Approximately one-third of patients with FTD have a family history or confirmed predisposing genetic component [29, 93]. Gene variants that have been linked with early-onset neurodegenerative processes (i.e., those occurring at <40 years of age) common to both FTD and NP-C include *C9orf72* [94, 95, 96, 97] and the progranulin gene, *PGRN*, which is associated with TAR DNA-binding rotein-43 (TDP-43)-related changes [29, 98]. Further, some forms of FTD can be listed alongside NP-C as tauopathies due to mutations in the *MAPT* tau gene on chromosome 17, and subsequent pathological tau accumulation [99, 100, 101, 102, 103]. Both NP-C and tau-related forms of FTD can display similar tau isoform profiles [102, 104].

Differential diagnosis of FTD *versus* NP-C is most likely to be required in adult patients who present with cognitive impairment and prominent executive dysfunction above 30 years of age, or in patients who present with major mental illness (e.g., schizophrenia-like symptoms, possibly with atypical signs) aged 15–30 years. Characteristic clinical manifestations that help distinguish NP-C from FTD and other forms of EOCD include both visceral and neurological

symptoms [10, 29]. Hepatosplenomegaly in NP-C has been proposed as a differential diagnostic indicator *versus* FTD and other etiologies associated with EOCD [29]. Abnormal saccadic eye movements (including VSGP) also serve as a strong indicator of possible NP-C [29].

There are relatively few published data on *NP-C* gene mutations from clinical screening studies in FTD patients. A genetic screening study including 133 FTD patients along with other neurodegenerative disorders did not detect any *NPC1/NPC2* gene variants [22]. Findings from an ongoing genetic screening analysis of *NPC1/NPC2* variants in 200 French FTD patients are awaited.

Despite the lack of supportive data, the degree of symptomatic overlap and emerging evidence of genetic and pathophysiological commonalities between NP-C and FTD suggest that the clinical FTD population could be a relevant niche for the detection of NP-C.

***Parkinsonism***

Parkinsonism is clinically defined by tremor, bradykinesia/akinesia, rigidity, and postural instability and occurs in numerous sporadic and inherited neurological diseases. It is described in a range of tauopathies, and is often associated with EOCD [105]. However, parkinsonism can be difficult to discern among other prevailing neurological symptoms that are common in NP-C [106]. For instance, some patients may be treated with neuroleptic drugs, and subsequently develop iatrogenic parkinsonism.

A cohort study of movement disorders in adults with NP-C reported mild parkinsonism (bradykinesia, axial rigidity, hypomimia and/or isolated rest tremor) in approximately 10% of patients [47]. In this series, it did not represent a key diagnostic feature, and was usually detected only after systematic neurological examination [47].

Substantial evidence from genetic studies indicates a possible association between impaired lysosomal function and parkinsonism. A number of Parkinson's disease (PD) genes (including *SNCA*, *LRRK2*, *parkin*, *PINK1*, and *ATP13A2*) are known to regulate lysosome-dependent pathways or lysosomal activity [107, 108, 109], while glucocerebrosidase (*GBA1*) mutations in GD patients and *SMPD1* mutations have been associated with PD [110, 111, 112, 113, 114, 115]. With reference to NP-C, the autophagy-lysosome pathway may be a contributory pathophysiological factor for PD [116]. Autopsy evidence from NP-C patients indicated aberrant phosphorylation and aggregation of synuclein-alpha protein in Lewy bodies, along with typical tau-related neuropathological features [59, 117].

Several reports have suggested potential links between parkinsonism and *NPC1/NPC2* mutations [22, 109, 118]. Two case series reported parkinsonism syndrome in a total of four patients with single heterozygous *NPC1* mutation [119]. A separate report of a heterozygous *NPC1* mutation carrier with PD-like symptoms was also described [120]. However, a large-scale genetic screening study in 563 European PD patients identified single heterozygous pathological *NPC1/NPC2* mutations in only 1.1% [22]. This was not significantly higher than in a control group (n = 7/846; 0.8%). No PD patients had homozygous *NPC1/NPC2* mutations, although 16 variants of unknown significance were detected (12 in *NPC1* and four in *NPC2*).

Overall, current evidence from clinical and genetic studies do not support parkinsonism as an important clinical niche for undetected cases of NP-C. More studies are needed to investigate whether *NPC1/NPC2* mutations might be found in younger patients with parkinsonism. The prevalence of NP-C gene variants among other, non-European cohorts has also not yet been established.

***Progressive supranuclear gaze palsy (PSP)***

PSP is a neurodegenerative disease characterized by VSGP, gait disturbance, akinetic-rigid syndrome with levodopa unresponsiveness, dementia and premature death [121, 122], and is classified clinically as a form of atypical parkinsonism [123]. VSGP combined with cognitive decline is considered pathognomonic for NP-C [7, 8, 10, 124, 125, 126]. Voluntary vertical saccades are affected first in NP-C, followed by reduced slow eye pursuit movements and impaired horizontal saccades, and over time, VSGP develops due to increasing brainstem neurodegeneration [127, 128, 129]. Between 65% and 81% of patients with NP-C have impaired saccadic eye movements, usually starting in the late-infantile period [10, 13, 32, 35]. Clinical cases of NP-C have been misdiagnosed as PSP [130, 131].

Approximately 40% of cases of PSP are associated with underlying tauopathic changes, and in this respect share pathophysiological aspects common to NP-C [121, 132, 133]. Many patients also show overlaps in the profile of clinical symptoms, particularly movement disorders and cognitive impairments [99, 121, 134]. This can present a challenge in differential diagnosis [131]. A key distinguishing factor between the two conditions is age at onset; PSP usually starts in the fifth to the seventh decade of life, while NP-C generally presents much earlier on.

The occurrence of NP-C within the clinical PSP population is unknown. A case series in four PSP patients reported filipin test results consistent with NP-C, but no genetic confirmation was established [36]. A genetic screening study in multiple neurodegenerative diseases, including 94 patients with PSP, did not detect any *NPC1/NPC2* variants [22]. Given the clinical similarities between NP-C and PSP, it is recommended that patients who present with PSP-like clinical signs before the ages typically associated with PSP should be tested for NP-C [135]. More specifically, the presence of cerebellar ataxia, EOCD with onset before 50 years of age, and/or visceral symptoms such as splenomegaly can help distinguish between PSP and NP-C [10, 44, 123]. Methods for assessing ocular motor abnormalities characteristic of PSP are available [136, 137]. Published data suggest that analysis of cerebrospinal fluid (CSF) truncated tau levels may also provide useful information for the differential diagnosis [138, 139].

No confirmed NP-C cases have been identified through any screening approaches in PSP to date. While PSP is considered less relevant as a potential clinical niche for undetected NP-C patients, further investigations in PSP are still considered scientifically reasonable.

***Organic psychosis***

NP-C, along with several other inborn errors of metabolism (IEMS), is among a large number of diseases associated with organic psychiatric disturbances [74, 87, 140, 141]. Psychiatric symptoms are most commonly observed in adolescent/adult-onset NP-C, and have been reported in up to 55% of patients in this category [7, 8, 19, 35, 47, 67, 70]. Notably, symptoms are often reported at initial presentation [47, 72]. In a study of 87 NP-C patients from the US national NP-C cohort, psychiatric problems were significantly more common

among patients aged ≥18 years (45%) compared with those aged <18 years (11%; $p < 0.01$) [35].

As seen in many diseases associated with organic psychiatric symptoms, NP-C patients who initially present in psychiatric practice may remain improperly diagnosed, or go undiagnosed, for years due to heterogeneous clinical features, limited awareness of NP-C as a possible underlying condition, and/or the long time frame over which the disease progresses [87]. Psychiatric symptoms may therefore be the only manifestation of NP-C for years before other symptoms become apparent [72, 142]. Consequently, patients who present to psychiatrists often experience significant delay before a definitive diagnosis of NP-C [7, 72, 87, 140].

Psychotic symptoms are the most frequent psychiatric manifestations reported in NP-C [19, 35, 47, 52]. and often manifest as schizophrenia-like symptoms comprising paranoid delusions, auditory hallucinations, and disorganized thoughts [7, 52, 72, 82, 140, 142]. Depression, bipolar disorder and obsessive-compulsive disorder are also reported [10, 19, 87, 141]. A retrospective survey of psychiatric presentations among French adult NP-C patients who underwent psychiatric evaluation reported psychotic symptoms in 55%, and half had a psychiatric diagnosis: schizophrenia in 27% and depression in 23% [19]. A systematic literature analysis of psychiatric manifestations in 58 NP-C patients who were mostly adolescents or adults at neurological onset reported psychotic symptoms in 62% overall, and behavior- and mood-related manifestations in 52% and 38%, respectively [18]. Notably, 87% of patients in the US NP-C cohort had learning difficulties, which are often also encountered in psychiatric practice [35].

There are few published data from genetic screening studies of NP-C in psychiatric patient populations. However, the 'ZOOM' study, which systematically screened for NP-C gene mutations in 250 patients with neurological and psychiatric symptoms, identified three (1.2%) new NP-C cases and 12 (4.8%) more patients who were classified as 'NP-C uncertain' [54]. The detection rate in this study was substantially higher than the general population, and suggests that screening for NP-C in selected neuropsychiatric populations may result in the identification of more new cases.

Vigilance for atypical psychiatric signs, neurological manifestations, and visceral symptoms can aid in the differential diagnosis of NP-C *versus* primary psychiatric conditions and other organic causes [140]. Readily recognizable psychiatric signs that should trigger the suspicion of underlying organic disease in patients with schizophrenia-like symptoms include: acute confusional states; a preponderance of visual hallucinations over auditory hallucinations; catatonia; early or acute onset of psychiatric symptoms; fluctuating symptoms; antipsychotic treatment resistance; and sensitivity to low doses of high-potency neuroleptics [7, 74, 82, 140, 143]. Clinical diagnostic algorithms provide a framework for the detection of hidden NP-C (amongst other IEMs) in psychiatric patient populations [74]. The NPC-SI may also be useful as a clinical screening tool in psychiatry [32].

Published evidence indicates that organic psychosis is an important clinical niche for NP-C screening. Improved awareness among psychiatrists of IEMs as possible causes of psychiatric symptoms is key to achieving early detection [70].

***Amyotrophic lateral sclerosis (ALS)***

ALS is a late-onset motor neuron disease featuring progressive neurodegeneration and a degree of symptomatic overlap with NP-C. Both NP-C and ALS can be associated with movement disorders, dysphagia, dysarthria, ophthalmoplegia and cognitive impairment/dementia [144, 145]. Between 5 and 10% of ALS cases are inherited in an autosomal dominant fashion [146]. The two conditions have a number of pathophysiological features in common, including tau-associated neurofibrillary tangles [145] and changes in intracellular second messengers [61, 147].

Despite clinical and neuropathological features held in common between ALS and NP-C, there are few published data indicating any firm clinical links. ALS is most common in individuals aged ≥60 years, but also occurs in younger patients [148, 149]. Nevertheless, based on the distinct overlap in clinical symptomatology in the two conditions (e.g., mild upper-girdle motor impairment with predominant VSGP, gait ataxia, dystonia and/or psychiatric features), it is considered most likely that NP-C would be detected among patients with young-onset ALS. In terms of differential diagnosis, electrophysiological testing is a widely used method for assessing motor neuron disease specific to ALS [150]. However, electrophysiological tests in patients with NP-C generally provide mixed findings [151]. Signs of acute denervation are often observed in ALS but are not common in NP-C.

Only one report of genetic screening for NP-C in ALS has been published to date. Whole-exome sequencing using NGS was conducted in two siblings who were suspected to have ALS, but were subsequently diagnosed with NP-C [23].

Overall, there is a paucity of published data on the occurrence of NP-C in the ALS population. Thus, without additional evidence, ALS cannot currently be considered a relevant clinical niche for NP-C.

***Chronic inflammatory CNS disease***

Multiple sclerosis (MS) occurs in approximately 180/100,000 in Central Europe and North America [152]. Common symptoms, which typically start during early adulthood and follow a relapsing or progressive course, include ataxia, optic neuritis, sensory disturbance, pyramidal weakness, bladder dysfunction, fatigue, insidious cognitive deterioration, and depression/euphoria.

Patients are routinely diagnosed with MS based on CSF analysis demonstrating intrathecal immunoglobulin synthesis, white-matter abnormalities on cerebral MRI, and evidence of demyelination [153, 154, 155]. In patients who present with typical clinical signs, the differential diagnosis is reasonably limited [153], but in less typical cases a wide range of rare causes must be considered.

There are several overlaps in the clinical symptomatology of NP-C and MS, particularly in terms of movement disorders (ataxia) [20, 156], oculomotor disturbances (slow saccades, impaired saccadic pursuit and VSGP) [34, 125, 128, 153, 157], and cognitive deficits [158, 159]. In addition, both NP-C and MS share a number of neuroinflammatory changes. Altered CSF neuroinflammatory cytokine marker levels, microglial activation and the release of neurotoxic cytokines have been reported in both conditions [160, 161, 162]. These are thought to be central pathogenetic features of MS, while their role in NP-C is not clear at present.

Screening for NP-C in patients with presumed MS is appropriate when cranial MRI findings are largely normal (i.e., not fulfilling accepted imaging criteria for MS), as is often the case in late-onset NP-C [153, 156, 163]. Similarly, the absence of chronic-inflammatory features from CSF analysis, persistent inefficacy of disease-modifying MS treatments, or normal visual evoked potentials should initiate further evaluation of potential differential diagnoses [151, 153].

One case of an adult patient with prominent progressive dementia and multiple non-specific neurological signs has been reported as 'adult-onset NP-C mimicking features of MS [164]. Neurological symptoms included slight bilateral ataxia in the legs and mild saccadic dysmetria, concomitant with behavioral, mood and early-onset cognitive impairments. While the patient was initially diagnosed with MS based on clinical findings, CSF analysis, and cranial MRI, persistent splenomegaly prompted further investigations that led to a diagnosis of NP-C [164].

Despite anecdotal evidence there are no robust published data to support MS as a relevant clinical niche for detecting NP-C. Further studies are required to develop the understanding of potentially overlapping disease mechanisms.

***Cholestasis and hepatosplenomegaly in early infantile patients***

The earliest presentation of NP-C during infancy may be with non-immune hydrops and fetal ascites and/or isolated splenomegaly [7, 8, 10, 165]. Infants may be born with prolonged, unexplained neonatal jaundice lasting >2 weeks, and acute liver failure [7, 10, 16, 17]. These symptoms precede any obvious neurological symptoms in the course of NP-C [6, 7, 8, 10, 13].

The differential diagnosis of cholestatic symptoms in pediatric patients is extensive [166, 167, 168, 169, 170, 171], and presents challenges for the identification of NP-C in pediatric liver units [172]. However, the vast majority, if not all patients with NP-C will have splenomegaly at birth. Pulmonary disease is a rare concomitant complication, but is another strong clinical indicator. Portal hypertension needs to be excluded in older children who present with cholestatic symptoms [17, 171].

NP-C has been reported as one of the most common genetic causes of liver disease during infancy [6, 10, 173, 174]. For example, in a UK study of infants investigated for acute liver failure, three cases of NP-C (8%) were identified among 37 patients with an IEM [173]. In a North American liver unit, NP-C alone accounted for approximately 8% of general pediatric patients who were investigated for neonatal cholestasis (n = 40) [174].

As visceral symptoms precede neurological symptoms in the course of NP-C, neonates and infants who present with visceral symptoms and concomitant neurological signs such as developmental delay, hypotonia, and gelastic cataplexy, are clear candidates for additional diagnostic testing [6, 10]. An early-onset NPC-SI facilitates the identification of patients with suspected NP-C aged ≤4 years of age, based on combinations of some of these key symptoms [175]. Patients who exhibit both cholestatic symptoms and splenomegaly show high SI scores (indicating strong suspicion of NP-C).

Genetic screening studies have demonstrated a possible enrichment for NP-C among cholestatic infants in the general clinical population. An NGS study with microarray re-sequencing analysis in 222 infants with cholestasis, acute liver failure, hepatomegaly and/or splenomegaly identified autosomal recessive IEMs in 19 patients (9%), and confirmed NP-C

in one (0.5%) [176]. Seven (3%) heterozygous individuals with single pathogenic *NPC1* variants were also reported [176]. In a study based on massively parallel sequencing of 93 genes associated with inherited cholestatic disorders in infants, a novel pathogenic *NPC1* mutation was identified [24, 177].

Overall, data indicate that patients with early cholestasis/prolonged neonatal jaundice and/or hepatosplenomegaly represent a highly relevant clinical niche for the detection of NP-C. Improved NP-C detection may help avoid inappropriate liver transplantation [30, 176, 177].

***Antenatal findings, fetal abnormalities and newborn screening***

Prenatal diagnosis and newborn screening for LSDs have become topics of intense research in recent years due to the development of targeted treatment options, improved screening methods and the availability of biomarkers [30, 198, 199, 200, 201].

In terms of early-infantile clinical symptoms, prolonged neonatal jaundice, splenomegaly (with or without hepatomegaly) and fetal ascites (hydrops fetalis) detected during antenatal assessment should arouse suspicion of NP-C, even in the absence of a family history [202, 203]. To date, 15 cases of antenatal-onset NP-C were reported: all featured splenomegaly, ascites, hepatomegaly and/or placentomegaly at a median gestational age of 24 weeks [203]. Unexplained fetal hydrops and signs of liver failure may be viewed as additional factors to raise suspicion of NP-C [10]. These clinical symptoms are nonspecific, and must be considered alongside other causes during differential diagnosis [24, 167, 172, 176]. The early-onset NPC-SI is available to support diagnosis based on clinical symptomatology in infants aged ≤4 years [32, 175].

As NP-C is inherited in an autosomal recessive manner, prenatal diagnosis is available to affected families if they wish, for the detection of NP-C among siblings of first cases to be diagnosed. Traditionally, filipin staining based on chorionic villus sampling was recommended for antenatal diagnosis of NP-C [10, 167, 204]. However, as genetic analysis is now routinely used in initial diagnostic workup, causative mutations are usually known in index cases, and mutation analysis based on chorionic villus sampling or amniocentesis is the method of choice for antenatal diagnosis. Simple testing for free fetal DNA in maternal blood may one day allow prenatal screening in affected families, thus avoiding invasive prenatal diagnostic procedures and risk of miscarriage. For previously undiagnosed prenatal-onset and neonatally presenting cases, it is likely that plasma and dried blood spot (DBS) biomarkers will become the preferred method for postnatal diagnosis and newborn screening of NP-C, particularly in cases with a strong clinical suspicion of NP-C, where only minor blood sample volumes are available [21, 30, 167, 200, 205, 206, 207]. Familial genetic analyses and direct gene sequencing are also strongly recommended in confirmed NP-C cases in order to identify as-yet undetected patients and carriers among family members [204].

For newborn screening, NGS and multi-gene panels will make rapid, wide-ranging genetic screening more accessible [21, 24, 176]. However, ethical concerns and legal restrictions may preclude genetic newborn screening in some countries [21, 208].

Overall, patients with certain fetal abnormalities are considered to be a highly relevant clinical niche for NP-C screening, and multi-panel approaches (e.g., with biomarkers) may prove especially helpful. While newborn screening offers tangible benefits in terms of early detection and diagnosis, more consideration of both practical and ethical implications is required.

## Discussion

In this review, twelve clinical niches considered to have a potential of harboring patients with an increased risk of NP-C were examined in detail via the published evidence and expert opinion. Niches with strong evidence to support their high relevance to detecting and diagnosing NP-C where it has previously been overlooked include: movement disorders (EOA and dystonia), organic psychosis, early-onset cholestasis/(hepato)splenomegaly, cases with relevant antenatal findings or fetal abnormalities, and patients affected by family history, consanguinity and endogamy. Niches thought to be of potential relevance, where further data are required and/or studies are still ongoing include: EOCD, FTD, parkinsonism, and chronic inflammatory CNS disease such as MS. Only relatively weak evidence was available to suggest an increased likelihood of detecting NP-C in ALS and PSP niches.

It is possible that other putative clinical niches may also yield further valuable data (e.g., other tauopathies, early-onset AD, multiple system atrophy, Huntington-like disease, treatment-resistant epilepsy, patients with one identified *NPC1 or NPC2* mutation). Screening initiatives within locally existing niche cohorts represent a good starting point for future studies.

Future screening studies in clinical niches identified here as carrying an increased risk of NP-C would address the following goals: 1) confirm whether *NPC1/NPC2* gene mutations underlie unclear symptomatology in suspected cases; 2) exclude NP-C in patients where, despite unclear symptomatology, it is not present; and 3) aid secondary identification of other relevant rare diseases for differential diagnostic purposes. The identification of hidden NP-C cases associated with unclear symptoms in at-risk patient groups is important because a targeted therapy (miglustat) is available that is of most benefit where treatment is initiated early on in the disease course [10, 204, 209].

This review of published evidence serves to highlight that, as in most ultra-rare diseases, consideration of clinical symptom combinations/co-morbidities relevant to each niche is a vital aspect for the detection of NP-C. For instance, throughout all niches where clinical neurological or psychiatric manifestations form part of the core symptomatic profile, historical cholestatic symptoms or hepatosplenomegaly, and/or ongoing visceral symptoms, whether symptomatic or not, are consistently acknowledged as strong factors in raising suspicion of NP-C. The NPC-SI and the early-onset NPC-SI allow a systematic approach to initial screening based on clinical symptomatology [32, 175]. Easy-to-apply and readily available tests such as oculomotor examinations and cranial MRI can add valuable further information (e.g., in organic psychosis, dystonia, EOCD, and unclear neuroinflammatory disease).

Rapid, convenient and cost-effective biomarker-based methods for NP-C screening and diagnosis are increasingly becoming available in specialized laboratories worldwide [21]. Numerous studies have demonstrated the utility of plasma oxysterols as a primary diagnostic test for NP-C across a number of patient cohorts [21, 25, 26, 210]. Lysosphingolipids have also been shown to be effective biomarkers for NP-C [21, 27, 28], additionally providing the advantage of adaptation to robust high-throughput setups using DBS filter cards and multiplex analysis of NP-C along with other sphingolipidoses (e.g., GD and Fabry disease). It is thought likely that combined analysis of both oxysterol and lysosphingolipid profiles will help to improve diagnostic specificity for NP-C *versus* other IEMs. Bile acid assays represent a promising additional biomarker option for NP-C screening/diagnosis [21, 29, 30]. While limited published data are available, an advantage of lysosphingolipid and bile acid-based methods is that they can be conducted in plasma samples or DBS. Studies utilizing some of

these biomarker methods are ongoing in some clinical niches addressed in this review (e.g., in dystonia, PSP, and early-onset cholestasis).

Improvements in the speed, accuracy, accessibility and cost-effectiveness of *NPC1/NPC2* analysis over the last decade have led to genetic analysis now being considered as the primary means of confirming NP-C diagnosis [21]. While Sanger-based cDNA and gDNA sequencing remains the mainstay of NP-C genetic analysis, NGS techniques, which can be adapted to gene panels and used in whole-exome and whole-genome sequencing, are increasingly being applied [21]. However, due to certain error rates inherent in all genetic approaches, complementary testing by MLPA and quantitative PCR can provide further proof [21, 54]. Data from studies utilizing NGS in certain NP-C clinical niches covered in this review have already been published (e.g., in EOA, ALS and early-onset cholestasis) [20, 23, 24]. Further data on the application of these techniques in prenatal testing and newborn screening/diagnosis are awaited [21].

## Conclusions

Several clinical niches have been identified that harbor patients at increased risk of NP-C. There is a continued need for improved awareness of NP-C as a possible underlying cause of symptoms commonly encountered in these niches. Increased vigilance for combinations of characteristic clinical disease manifestations, along with the inclusion of NP-C in biomarker and genetic screening assays, could reduce diagnostic delays and result in earlier initiation of targeted therapy for patients with NP-C.

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