Movement Disorders
CLINICAL PRACTICE

CASE SERIES WITH LITERATURE REVIEW

Niemann Pick Type C Presenting as Familial Late-Onset Richardson Syndrome. A Case Series of Four Siblings

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Abstract: Background: Niemann Pick Type C (NP-C) is a rare lysosomal disorder, characterized by clinical heterogeneity. Late age of onset (> 40 years) is exceedingly rare, with approximately 20 reports to date. Herein, we describe four siblings with disease onset over 40 years of age.

Cases: Two of the siblings fulfilled criteria for probable PSP with Richardson syndrome (PSP-RS), whereas the remaining cases had atypical clinical features, with prominent cerebellar symptoms and overt frontal-executive dysfunction, fulfilling criteria for probable PSP-RS and probable PSP with predominant frontal presentation (PSP-F). All patients reported hearing loss. DaT-scans were normal in two of the cases, and midbrain atrophy was absent. EEG was abnormal, with generalized paroxysms and short sequences of delta slow waves in one of the cases. All patients had a homozygous point mutation c.2861C>T, p.(Ser954Leu) in the *NPC1* gene.

Literature review: A literature review supported the association between the c.2861C>T, p.(Ser954Leu) mutation in the *NPC-1* gene and late-onset NP-C. Cerebellar signs, early-onset hearing loss, normal DaT-scan and absence of midbrain atrophy in brain MRI are red flags for a PSP diagnosis and should prompt further investigations for alternative diagnoses, including NP-C.

Conclusions: Late onset (>40 years) NP-C, particularly due to c.2861C>T, p.(Ser954Leu) mutation in the NPC-1 gene, can mimic Richardson syndrome.

Niemann Pick Type C (NP-C) is a rare autosomal recessive neurovisceral lysosomal disorder, characterized by abnormal cellular lipid trafficking. It is caused in most cases (~95%) by mutations in the *NPC1* and a minority of cases (~5%) by mutations in the *NPC2* gene.[1] The encoded proteins appear to participate in post-lysosomal and late endosomal glycolipid and cholesterol transport, which results in their accumulation in the lysosomal system.

Traditionally, NP-C is classified based on age at onset of neurological or psychiatric symptomatology into pre- and peri-natal (<3 months), early-infantile (<2 years), late-infantile (<6 years), juvenile (<15 years) and adolescent/adult (>15 years).[2]

NP-C is characterized by great clinical heterogeneity, including visceral signs (hepato- and splenomegaly), cortical signs (cognitive deficits, neuropsychiatric symptoms, epilepsy), and subcortical (or "deep brain") signs which include supranuclear gaze palsy, dysarthria, dysphagia, cerebellar ataxia, cataplexy and movement disorders (chorea, myoclonus, tremor).[2] Age at disease onset is the main determinant of clinical presentation, with younger age at onset characterized by predominant visceral

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symptoms and older age by cognitive and psychiatric manifestations.[1] Age at onset is also the most important factor determining the natural course of NP-C patients, with earlier disease onset usually associated with more rapid disease progression and poorer survival.

NP-C is rare, with an estimated prevalence of one case every 100,000 to 150,000 live births.[3] More recent data, based on analysis of exome sequencing databases, have estimated the incidence of late-onset forms at ~1/20,000 to 1/40,000, indicating that NP-C is frequently mis- or undiagnosed.[4] Adult-onset NP-C represents 20–30% of all NP-C cases.[5] NP-C cases with an age at disease onset of over 40 years are exceedingly rare, with about 20 patients described to date.[6–19] A 2007 review of the adult form of NP-C reported five patients with an age at disease onset of ≥40 years, among 68 cases.[6] Subsequent single cases have been reported, which present significant clinical heterogeneity, with a recent study reporting a patient with a Richardson syndrome presentation, with disease onset at 69 years.[19]

Herein, we describe a family of four siblings with late (>40 years) onset of neurological manifestations, with probable PSP-RS.

Case Series

Demographic, clinical, neuropsychological and paraclinical findings are summarized in Table 1. The family tree is presented in Figure 1.

Case 1

A 60-year-old female presented with a 7-year history of dysarthria, which had remained relatively stable over the initial 5 years. She had sporadic falls over the past 1.5 years due to mild ataxia. Over the past year she complained about anxiety with sleep difficulties, poor attention, memory deficits and rare episodes of disorientation in time. She was initiated on donepezil and trazodone, with minimal effect. She reported hearing loss and hyposmia, without being able to identify the time of onset.

Neurological examination revealed mild axial rigid bradykinetic parkinsonism with limb hypotonia. She had a small-amplitude, shuffling gait with mild camptocormia and decreased arm swing. Postural reflexes were abnormal. She exhibited upper-limb action tremor with mild dysdiadochokinesia. Plantar reflexes were extensor, without other pyramidal signs. She had a frontal syndrome with primitive reflexes, utilization behavior and facilitatory paratonia. She exhibited supranuclear gaze palsy, with decrease in amplitude and velocity of vertical saccades, with normal horizontal saccades. The patient fulfilled criteria for "probable PSP Richardson syndrome (PSP-RS)," with vertical supranuclear gaze palsy and repeated unprovoked falls, which correspond to high level of certainty in the core functional domains "ocular motor dysfunction" (O1) and "postural instability" (P1).

Neuropsychological evaluation was consistent with a predominantly frontal-dysexecutive syndrome, intact memory, mild visuospatial/visuo-constructive deficits and moderate overall cognitive decline (MMSE: 25/30; 20th age/education-adjusted percentile).

Brain MRI exhibited parietal>frontal, left>right cortical atrophy (Fig. 2A,B), with no midbrain or superior cerebellar peduncle atrophy (Fig. 2D). DaT-scan was normal (Fig. 2C). HMPAO-Spect exhibited bilateral frontotemporal hypoperfusion, R>L. Her EEG was abnormal, with generalized paroxysms and short sequences of delta slow-waves of large amplitude, without laterization. Her abdominal ultrasound was negative for liver or spleen enlargement. Sensory/motor conduction studies and needle electromyography were within normal limits. Measurement of Lysosphingomyelin-509 by liquid chromatography mass spectrometry was within normal limits (result: 0.5 ng/ml; reference <0.9 ng/ml). Whole-exome sequencing followed by Sanger sequencing revealed a homozygous point mutation NM_000271.5 (*NPC1*): c.2861C>T, p.(Ser954Leu) in the *NPC1* gene.

Case 2

This 67-year-old female, with a medical history of hypercholesterolemia, hypothyroidism and depression under treatment, reported repeated falls over the previous 2 years. Additional symptoms included irritability, verbal aggression and mood swings. She also exhibited cognitive decline, with word-finding difficulties and palilalia in addition to urinary incontinence and dysphagia. She reported progressive decrease in hearing acuity starting at age 55–60, requiring a hearing aid.

At neurological examination, the patient could not walk unassisted, due to severe postural instability with retropulsion. Postural reflexes were abnormal. Pivoting was present when turning. Axial rigidity was present, with no bradykinesia or involuntary movements. Primitive reflexes were elicited with facilitatory paratonia. She had a right extensor plantar reflex, without other pyramidal signs. She had severe vertical supranuclear gaze palsy with normal horizontal saccades. She had multiple square wave jerks (>15/min) and reduced blinking rate (0 blinks/min). The patient fulfilled criteria for "probable PSP Richardson syndrome (PSP-RS)" as well as "probable PSP-F" (PSP with predominant frontal presentation). She exhibited vertical supranuclear gaze palsy, repeated unprovoked falls and frontal cognitive/behavioral presentation, which correspond to high level of certainty in the core functional domains "ocular motor dysfunction" (O1) and "postural instability" (P1), as well as moderate level of certainty in the functional domain "cognitive dysfunction" (C2).

She exhibited severe overall cognitive decline (MMSE 12/30; 10th age/education-adjusted percentile, ACE-R 26/100; 5th age/education-adjusted percentile), with pronounced frontal-executive dysfunction and moderate visuospatial deficits. Her baseline MRI was unremarkable (Fig. 2E,F), whereas a follow-up MRI (2 years after the initial MRI) exhibited mild parietal atrophy (Fig. 2G). DaT-scan was within normal limits. Her EEG was normal. An abdominal ultrasound did not reveal hepatosplenomegaly. She underwent targeted Sanger sequencing, which revealed a homozygous point mutation NM_000271.5 (*NPC1*): c.2861C>T, p.(Ser954Leu) in the *NPC1* gene.

TABLE 1 *Demographic, clinical, neuropsychological and paraclinical characteristics of patients*

	Patient 1	Patient 2	Patient 3	Patient 4
Demographic/clinical data				
Sex	Female	Female	Female	Male
Age	60	67	63	56
Disease duration (y)	14	4	10	8
Age at disease onset	46	63	53	48
Presenting symptom	Dysarthria	Imbalance, falls	Cognitive deficits	Imbalance, falls
Neurological signs				
VSSP	(+)	(+)	(+)	(+)
VSGP	(+)	(+)	(+)	(−)
Cerebellar signs	(+)	(−)	(−)	(+)
Parkinsonism	Axial, rigid akinetic	Axial, rigid-akinetic	Axial, rigid-akinetic	(−)
Pyramidal signs	(+)	(+)	(−)	(−)
Dystonia	(−)	(−)	(−)	(−)
Myoclonus	(−)	(−)	(−)	(−)
Chorea	(−)	(−)	(−)	(−)
Dysarthria	(+)	(+)	(−)	(+)
Dysphagia	(−)	(+)	(−)	(−)
Urogenital symptoms	(−)	Urinary incontinence	(−)	(−)
Dementia	Frontal-dysexecutive	Frontal- dysexecutive	Frontal-dysexecutive	Frontal-dysexecutive
Psychiatric symptoms	Anxiety	Irritability, aggressivity, mood swings	Emotional liability	
Hearing loss	(+)	(+)	(+)	(+)
Primitive signs	G, S, P	G, S, P	G, S, P	
Neuropsychological profile				
MMSE	25/30	12/30	19/30	21/30
FAB	9/18	3/18	6/18	6/18
5 WR del	5/5	1/5	NA	NA
Clox 2	11/15	9/15	NA	NA
Laboratory tests				
Cortical atrophy	Parietal > frontal	(−)	Diffuse (predominantly parietal)	Diffuse (predominantly parietal)
Midbrain surface (mm^2)	150	127	115	117
SCP width (mm)	2.9	3.0	2.7	2.8
DaT-scan	Normal	Normal	NA	NA
EEG	Abnormal	Normal	NA	NA
Hepatosplenomegaly	(−)	(−)	NA	NA

Case 3

A 63-year-old woman reported a history of mild cognitive deficits initiating 10 years ago. During the following year (54 years ago) she also exhibited impaired walking with imbalance and frequent falls. During the last 6 years she had needed unilateral walking aid. She gradually developed emotional liability and a restriction in downward gaze. Her medical history included

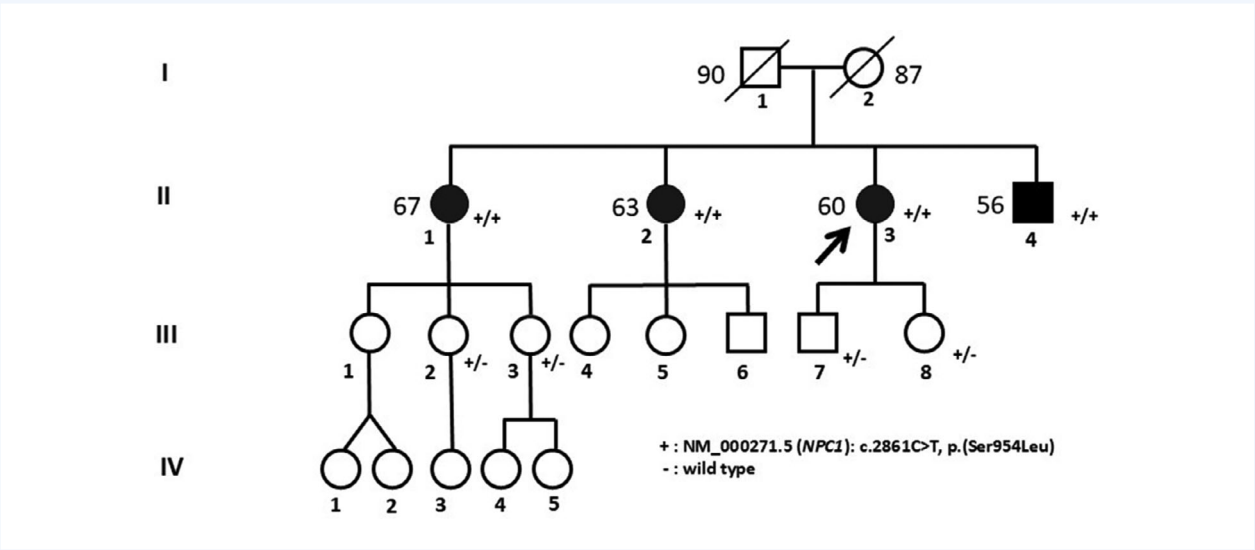

Figure 1. Family tree. Index patient (patient 1) is marked with an arrow. 5 WR del, 5-word delayed recall test; Clox 2, 15-point clock drawing test (copy); FAB, frontal assessment battery; MMSE, mini mental state examination; NA, not available; P, palmomental; primitive signs G, grasp; S, snout; VSGP, vertical supranuclear gaze palsy; VSSP, vertical supranuclear saccade palsy.

hyperlipidemia treated with atorvastatin, as well as hearing loss starting approximately from the age of 45.

At neurological examination, she exhibited camptocormia and severe postural instability (Pull test + scoring 3 out of 4). She was able to walk using a unilateral walking aid. She also exhibited axial but no appendicular rigidity and she did not present bradykinesia or other signs of parkinsonism. Deep tendon reflexes were normal. She also exhibited frontal release signs including grasping. Eye examination revealed vertical (downward) gaze palsy and frequent square wave jerks. The patient fulfilled criteria for "probable PSP Richardson syndrome (PSP-RS)," with vertical supranuclear gaze palsy and repeated unprovoked falls, which correspond to high level of certainty in the core functional domains "ocular motor dysfunction" (O1) and "postural instability" (P1).

Neuropsychological testing showed moderate cognitive deficits with a relative sparing of memory (MMSE 19/30; 10th age/education-adjusted percentile), apraxia (mainly evident in pantomime examination) and severe impairment in frontal-executive functions (FAB 6/18; 5th age/education-adjusted percentile).

Her MRI scan showed generalized cortical atrophy, more pronounced parietally, without brainstem atrophy (midbrain surface 115 mm^2, SCP width 2.7 mm) (Fig. 2H,I). Due to the positive family history, the patient underwent targeted Sanger sequencing, which revealed a homozygous point mutation NM_000271.5 (NPC1): c.2861C>T, p.(Ser954Leu) in the *NPC1* gene.

Case 4

A 56-year-old man was initially examined at age 54, reporting initial symptoms at 48 years of age, with gradual loss of balance while walking resulting in frequent falls. Concomitant cognitive decline was also described. His medical history included hearing loss since childhood, hepatitis B virus infection under treatment and polycystic renal disease which eventually led to kidney transplantation a year ago.

At neurological examination a bizarre ataxic walking pattern was observed. Postural reflexes were mildly impaired (scoring 1 out of 4). Dysarthric speech, upper limb dysmetria and coordination impairment were also noticed. Deep tendon reflexes were normal, and plantar response was flexor bilaterally. No appendicular parkinsonism was observed. Moreover, he exhibited slow vertical saccades and a typical "around-the-house" sign when attempting to turn his gaze downwards. The patient fulfilled criteria for "probable PSP Richardson syndrome (PSP-RS)" as well as "probable PSP-F" (PSP with predominant frontal presentation). He exhibited slow velocity of vertical saccades, repeated unprovoked falls and frontal cognitive/behavioral presentation, which correspond to high level of certainty in the core functional domain "postural instability" (P1), as well as moderate level of certainty in the functional domains "ocular motor dysfunction" (O2) and "cognitive dysfunction" (C2).

Neuropsychological testing showed moderate cognitive deficits (MMSE 21/30; 10th age/education-adjusted percentile, ACE-R 70/100; 5th age/education-adjusted percentile) and severe impairment in frontal-executive functions (FAB 6/18; 5th age/education-adjusted percentile). He also presented moderate speech and visuospatial/visuo-constructive deficits with relative sparing of memory.

The patient underwent an MRI scan, which showed diffuse cortical atrophy, most prominent in the parietal lobes (Koedam 2), without brainstem atrophy (midbrain surface 117 mm^2, SCP width 2.8 mm) (Fig. 2J,K). CSF biomarkers of neurodegeneration (Aβ42,

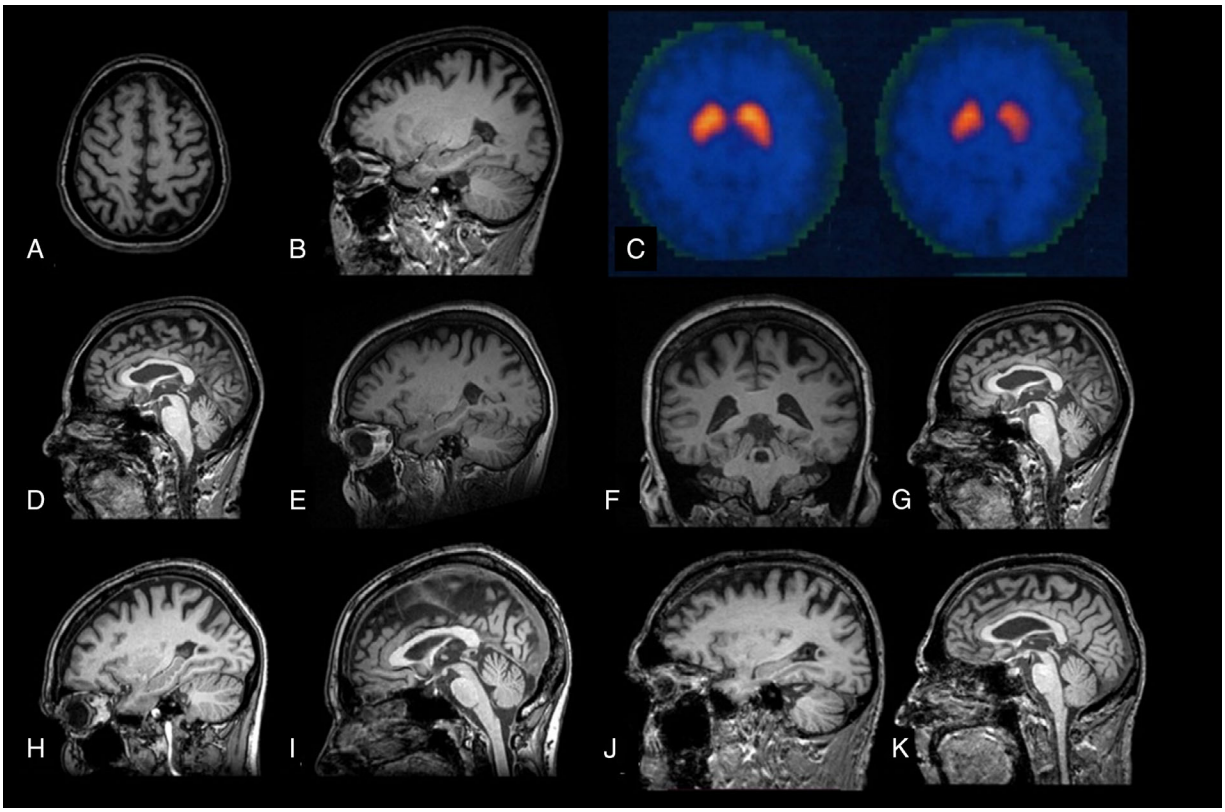

Figure 2. Imaging data of patients (all MRI images are T1-weighted). Patient 1 (A-D): axial image exhibiting left>right, primarily parietal atrophy (A); sagittal image illustrating parietal>frontal cortical atrophy (B); DaT-scan without evidence of nigrostriatal denervation (C); midsagittal image with no evidence of midbrain atrophy (D); Patient 2 (E–G): basiline sagittal image with no evidence of cortical atrophy (E); coronal image with no evidence of atrophy (F); follow-up MRI (2 years after initial scan) indicating mild parietal>frontal atrophy (G); Patient 3 (H–I): Sagittal image with parietal>frontal cortical atrophy (H); Normal brainstem morphology at midsagittal image (I); Patient 4 (J, K): Sagittal image with diffuse cortical atrophy (J); midsagittal image with normal brainstem appearance (K).

t-tau, p-tau 181) were not indicative of Alzheimer's disease. He also underwent targeted Sanger sequencing, which revealed a homozygous point mutation NM_000271.5 (NPC1): c.2861C>T, p.(Ser954Leu) in the *NPC1* gene.

Literature Review

NP-C is a rare disease, mostly affecting infants, juveniles or young adults. Disease onset at >40 years of age is exceptionally rare, with about 20 patients described to date.[6–19] Clinically, NP-C is characterized by great heterogeneity, presenting with visceral, neurological and psychiatric symptoms. Due to this phenotypical heterogeneity, NP-C either is diagnosed with a significant delay of >5 years or remains undiagnosed altogether.[6]

Among neurological symptoms, vertical supranuclear saccade palsy (VSSP), followed by vertical supranuclear gaze palsy (VSGP), is of particular importance in the diagnosis of NP-C, due to its specificity.[20] Studies have supported that VSSP in NP-C can precede other focal neurological signs even by decades, highlighting the importance of a thorough neuro-opthalomological examination in suspected cases.[21] Of importance, VSGP is a rare neurological manifestation, most commonly associated with progressive supranuclear palsy, with other diseases being exceedingly rare (eg, Gaucher disease).[22,23] Thus NP-C enters the differential diagnosis of PSP, with the most recent PSP diagnostic criteria supporting the exclusion of NPC in cases with age at disease onset of <45 years.[22]

Herein we describe four siblings with a Richardson syndrome presentation, with an age of disease onset >40 years. Importantly, two of the four siblings fulfilled criteria for "probable PSP-RS," without atypical clinical features, whereas the other two siblings had a more atypical or mixed presentation, fulfilling criteria for both "probable PSP-RS" and "PSP-F." To date, to the best of our knowledge, only five other reports of PSP-RS presentation of NP-C with an age of onset over 40 years of age have been published. The clinical characteristics of these patients are summarized in Table 2.

TABLE 2 *Clinical and genetic characteristics of patients with NP-C presenting with late-onset (>40 years) PSP-RS published previously*

Case	Sex	Age (y)	AAO (y)	First symptoms	Eye movement abnormalities	Postural reflexes	Parkinsonism	Speech	Cognitive status	Pyramidal signs	Cerebellar signs	Additional signs	Variation
1[9]	F	52	48	Imbalance, falls, dysarthria, dysphagia, cognitive impairment	VSSP, VSGP, "round the house" sign, Normal smooth pursuit and VOR	Markedly impaired	Rigidity (−) Bradykinesia (+) Tremor (−)	Cerebellar and pseudobulbar dysarthria	MMSE 29/30	Brisk reflexes	Mild ataxia	Sensorineural hearing loss	Compound heterozygous NPC1 (c.2861C>T, p.S954L; and c.3019C>G, p.P1007A)
2[14]	F	51	47	Falls, speech difficulties, mild memory deficits	VSSP, VSGP, normal VOR	NA	NA	Dysarthria unspecified	Executive dysfunction (verbal fluency; confrontational naming)	Brisk reflexes	Wide-based gait	Motor impersistence Mild generalized chorea	Homozygous NPC1 (c.2861 > T, p.S954L)
[40]	F	61	48	Wide-based gait, imbalance	VSSP, VSGP, "round the house" sign, abnormal vertical OKN, normal convergence	Normal	Hypomimia mild rigidity mild bradykinesia	spastic and cerebellar dysarthria	MOCA 22/30 multidomain deficits	Spastic dysarthria	Unstable gait, cerebellar dysarthria	(−)	Compound heterozygous NPC1 (c.2974G>C) (p.G992R); and c.3182 T>C (p.I1061T)
4[18]	F	67	62	Imbalance, falls	VSSP, eyelid opening apraxia (−) nystagmus (−) skew deviation (−)	Postural instability	Bradykinesia without decrement, rigidity (−)	NA	Applause sign (+), pseudobulbar affect	(−)	Mild to moderate appendicular and axial ataxia	(−)	Compound heterozygous NPC1 (c.180G>T), p.G60H; and c.3182 T>C, p.I1061T
5[19]	F	71	69	Imbalance, falls	VSGP	Postural instability	Freezing of gait	NA	Frontal-subcortical and visual deficits	(+) unspecified	Cerebellar ataxia	Postural myoclonic tremor	Compound heterozygous NPC1 (c.2819C>T, p.S940L); and (c.1976C>T, p.A659V)

Abbreviations: MMSE, mini mental state examination; NA, not available; OKN, optokinetic nystagmus; VOR, vestibulo-ocular reflex; VSGP, vertical supranuclear gaze palsy; VSSP, vertical supranuclear saccade palsy.

Our study supports that a high index of suspicion for NP-C in patients with PSP-RS, presenting in their fifth decade, is warranted. In these cases, a thorough familial history of neurological, visceral and psychiatric disorders should be obtained. Additionally, the presence of atypical clinical features, in particular hearing deficits and cerebellar signs should prompt an investigation for NP-C.

All of our patients exhibited hearing loss prior to onset of neurological symptoms. Hearing loss preceded other symptoms by many years and was present since childhood in one patient. Hearing deficits in NP-C have been reported, although a systematic study of these deficits is lacking. A study focusing on audiologic profiles of 28 NP-C patients reported abnormal auditory brainstem responses in 53%, abnormal acoustic reflex studies in 85% and abnormal pure-tone studies in 75% of patients.[24] Another study including three NP-C patients with no hearing deficits clinically, exhibited abnormal brainstem auditory evoked potentials in all patients, indicative of damage of the auditory pathway from the auditory nerve to the brainstem.[25] These data imply that hearing deficits may be under-reported in NP-C patients, and formal audiological and electrophysiological tests, including brainstem auditory evoked potentials, could assist in an NP-C diagnosis. Our patients exhibited clinically hearing loss, although we did not perform formal electrophysiological testing.

Cerebellar signs have rarely been present in PSP, although overt cerebellar ataxia is highly atypical and should prompt further investigations. There have been reports of neuropathologically confirmed PSP patients with predominant cerebellar ataxia, termed PSP-C.[26] However, given the rarity of significant cerebellar dysfunction in typical PSP, the presence of such semiology should alert the clinician for alternative diagnoses, including NP-C.

In addition to atypical clinical features, our patients had atypical findings in their paraclinical investigations. Firstly, two of our patients had a normal dopamine transporter SPECT (DaT-scan). Data regarding dopamine transporter imaging in NP-C patients is scarce, with reports of both normal and abnormal dopamine transporter density.[9,13,27] DaT-scan in PSP is practically always abnormal even at early disease stages.[28] Thus, in cases of PSP-RS with normal DaT-scan, further investigations are warranted for alternative diagnoses, including NP-C.

An additional atypical feature in our patients was the lack of significant midbrain atrophy, with midbrain surface >100 mm^2 in all patients, even on follow-up MRIs. Patients with PSP-RS usually present with midbrain atrophy, as indicated by surfaces of <100 mm^2.[29,30] These differences notwithstanding, midbrain atrophy exhibits significant variability among PSP patients. A single study has included MRI morphometric data in NP-C patients, which reported no midbrain atrophy.[31] Thus, lack of midbrain atrophy should be considered a red flag for a PSP diagnosis and prompt further tests.

Lastly, the EEG of one of our patients was abnormal, with generalized paroxysms and short sequences of delta slow waves of large amplitude. Several studies have supported the presence of diffusely abnormal EEG in NP-C patients,[6,32,33] although cases with normal EEGs have also been reported.[6,27,34] EEG abnormalities have also been reported in PSP, with initial studies supporting the presence of both background slowing and Frontal Intermittent Rhythmic Delta Activity (FIRDA) in a cohort of 12 PSP patients.[35] EEGs deteriorated with disease progression in most instances, with four patients (25%) exhibiting polymorphic theta and delta waves both frontally and temporally. Another study focusing on quantitative EEG in six PSP patients reported EEG slowing mainly in frontal regions, consistent with the predominantly frontal dysfunction evident in most PSP patients.[36] A study focusing on EEG patterns in early-stage PSP patients, highlighted the presence of background slowing, frontal slow waves and FIRDAs in PSP.[37] Thus, the presence of paroxysmal, high-amplitude delta slow-waves is atypical for PSP, which more commonly presents with generalized background slowing and frontal slowing.

Another noteworthy and highly atypical feature of the family described herein, considering NP-C's autosomal recessive inheritance, is the fact that all four siblings were affected. The probability of such a scenario is 1/256. An alternative explanation would be that one of the patients' parents was homozygous for an NPC mutation, which would result in a probability of 1/16 for all siblings to be homozygous for NPC mutations. However, according to the family history, both parents were asymptomatic, with an age of death at 90 and 87 years for the father and mother, respectively.

All of the patients described herein were homozygous for a known pathogenic variant causing NP-C [c.2861C>T, p.(Ser954Leu)], which has been described elsewhere.[9,14,16,38,39] Most previously described patients with this variant had a late-onset (>40 years) presentation with a PSP-RS,[9] corticobasal syndrome/ Balint syndrome,[38] or selective VSGP,[39] although earlier age of disease onset has also been described.[38] A patient homozygous for this variant had a disease onset at 51 years of age, with a PSP/bvFTD syndrome with exceptionally slow disease progression.[14] The presence of c.2861C>T, p.(Ser954Leu) variant in homozygous state correlated with an advanced age of disease onset in a single-center cohort.[16] Our findings reaffirm the notion that the c.2861C>T, p.(Ser954Leu) *NPC1* mutation correlates with advanced age at disease onset, particularly when homozygous.

Discussion

Herein we describe four siblings with NP-C, presenting with a PSP-RS phenotype. This study furthers our understanding of NP-C, highlighting the importance of clinical vigilance for clinical and paraclinical atypical features ("red flags") in patients with a running diagnosis of PSP-RS. A positive familial history of neurological or psychiatric disease, the presence of cerebellar signs or hearing deficits, normal dopamine transporter imaging studies, absence of overt midbrain atrophy in MRI and diffusely abnormal EEG should prompt further investigations for alternative diagnoses, including NP-C, even in patients with an age of

disease onset >40 years. Among different mutations in the *NPC1* gene, the c.2861C > T, p.Ser954Leu mutation, particularly in a homozygous state, can result in an unusually advanced age at disease onset.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Data Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

V.C.C.: 1A, 1B, 1C, 2A, 2C, 3A.
C.K.: 1A, 1B, 1C, 2A, 2C, 3A.
A.K.: 1A, 2C, 3B.
E.P.: 2A, 2B, 2C.
C.M.: 2A, 2B, 2C.
G.A.: 2A, 2B, 2C.
F.K.: 2A, 2B, 2C.
A.D.: 2A, 2B, 2C.
C.K.: 2A, 2B, 2C.
N.R.: 2A, 2B, 2C.
Z.K.: 2A, 2B, 2C.
E.L.: 2A, 2B, 2C.
N.T.: 2A, 2B, 2C.
G.K.: 2A, 2B, 2C, 3B.
G.K.: 2A, 2B, 2C, 3A, 3B.
E.K.: 1A, 2C, 3B.
N.S.: 1A, 2C, 3B.
L.S.: 1A, 2C, 3B.
S.G.P.: 1A, 2C, 3B.

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Disclosures

Ethical Compliance Statement: Written informed consent was obtained from patients or next of kin caregivers in cases of compromised mental capacity for use of anonymized personal data for publication. The study was performed according to the ethical guidelines of the 1964 Declaration of Helsinki. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

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