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Late adult-onset Niemann Pick type C (NPC): An "atypical" typical presentation at the age of 62

M. Sousa [a,b], B. Maamari [a], T. Bremova [a,c], J.M. Nuoffer [c,d], R. Wiest [e], D. Amstutz [a,b], P. Krack [a], D. Bartholdi [f], G. Tinkhauser [a,*]

[a] Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[b] Graduate School for Health Sciences, University of Bern, Switzerland
[c] Center for Rare Disorders, Institute of Clinical Chemistry Inselspital, Bern University Hospital, University of Bern, Switzerland
[d] University Children's Hospital Pediatric Endocrinology, Diabetology and Metabolism, Bern, Switzerland
[e] Department of Neuroradiology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[f] Department of Human Genetics, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland

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Case report

We report a 67-year-old woman with a 5-year history of progressive walking and balance difficulties with near-fall episodes. Gradually she also developed fine motor and speech problems that progressively impacted her communication. Swallowing function was unremarkable, and there was no history of choking episodes in the past. She had an uneventful neonatal period, with normal psychomotor development and unremarkable family history. Past medical history was positive for status post-cholecystectomy, hypertriglyceridemia, gastric bypass surgery (obesity) and mild obstructive sleep apnea. There was no history of hypertension, hypercholesterolemia or diabetes. Patient quitted smoking >5 years ago (23 packs/y).

On examination (video-1), she had a vertical supra-nuclear saccadic palsy (VSSP) without eyelid opening apraxia, nystagmus, skew deviation or pupillary abnormalities. She had no hearing or visual deficits. There was no muscle weakness, and sensory examination was unremarkable. Finger tapping was bilaterally slow but without clear sequence effect. No axial or appendicular rigidity was noticeable. Mild to moderate apendicular and axial ataxia were observed, and postural instability was present in both antero-posterior and medio-lateral directions. During walking, she had a mildly widened base and bilateral reduced arm-swing.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2023.105460

There was an asymptomatic drop in systolic blood pressure (>30 mmHg) immediately after standing-up that quickly recovered after 5 min standing. Urinary incontinence or other dysautonomic features haven't been found.

The neuropsychological assessment indicated mild perseveration (positive applause-sign) and mild depressive, anxious and apathetic symptoms. Additionally, difficulties in controlling emotions suggestive of pseudobulbar affect were noticed.

Brain MRI is depicted in figure-1. A previous abdominal CT, conducted for an epigastric pain episode, evidenced splenomegaly (14.5 cm [<12 cm]) with a normal-sized liver.

Antibody testing for anti-GAD, anti-endomisium, anti-transglutaminase and paraneoplastic panel (CRMP5, Amphiphysin, Ma2/Ta, Ri, Yo, Hu) were negative. CSF analysis was unrevealing apart from a mild protein elevation (0.70 g/L[0.20–0.40]).

Phenotypically our case fits in the Progressive Supranuclear Palsy (PSP)-like spectrum, with VSSP, gait and balance abnormalities and frontal lobe deficits. Nevertheless, there were important clues suggesting we were facing a different condition. Namely, the presence of cerebellar ataxia, which has only rarely been reported in PSP, the splenomegaly, and the cerebellar atrophy in the absence of clear

* Corresponding author. Department of Neurology, Bern University Hospital, Freiburgstrasse, 3010 Bern, Switzerland.
E-mail address: gerd.tinkhauser@insel.ch (G. Tinkhauser).

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imaging findings suggestive of PSP. Spinocerebellar ataxias (in particular SCA2 and SCA3), can present with ocular motility abnormalities, parkinsonism and dysautonomic features, however VSSP and cognitive abnormalities, as well as the negative family history make this possibility less likely. There were no additional signs suggesting a mitochondrial disorder (like short-stature, impaired hearing/vision, chronic progressive external opthalmoplegia, diabetes, etc). Anti-Iglon5 disease could present similarly, however the absence of sleep-disorders and the presence of splenomegaly is not common. Lastly, structural lesions involving upper brainstem region, cerebellum, basal ganglia, or respective afferent and efferent pathways can theoretically mimic this phenotype, but the progressive pace of the symptoms and remaining ancillary exams do not support this hypothesis.

Therefore, the hypothesis of alternative diagnosis including neurometabolic disorders such as Niemann Pick type C (NPC) and Gaucher's disease should be considered in such cases, even above 60-years-of-age [1]. The involvement of ocular vertical system instead of the horizontal makes NPC more likely.

The Niemann-Pick suspicious index was 185 (≥70 indicating strong suspicious). Plasma oxysterols (Cholestan-3b,5a, 6b-triol and 7-Ketocholesterol) were elevated with values of 53 μg/L and 125 μg/L ([<40and < 75], respectively) and reconfirmed in a separate sample. Subsequent genetic analysis for *NPC1* confirmed compound heterozygosity for c.180G > T/p.Gln60His, classified as variant of uncertain significance (VUS); and c.3182T > C/p.Ile1061Thr classified as pathogenic variant. Previous *in-silico* predictions of this VUS with PolyPhen2, SIFT, and Mutation Taster interpreted this variant as likely causative for NPC in two of these tools [2–4].

The majority of adult-onset forms are diagnosed within the 2nd and 3rd decade, yet there is an increasing number of reported cases starting after 50 years [3,5]. To the best of our knowledge, this is the latest manifest case of NPC reported. Previously, the latest case reported had symptom-onset at 54 years [6], and presented a more severe phenotype, with prominent cognitive dysfunction and chorea. In Table 1, we present a detailed description of NPC patients reported in literature with onset after the age of 40. The present patient had a milder phenotype, but shared similar MRI findings including cerebellar atrophy and periventricular signal intensities in T2-weighted images as well as increased CSF protein. In fact, focal changes in grey matter were suggested to be more apparent in adults due to less severe biochemical abnormalities [7]. Similar distribution of the T2 hypersignal lesions have been reported in another patient with onset of the symptoms at the age of 46 (Table 1) [8]. Therefore, we argue that the cribriform lesions seen in the basal ganglia and dentate nucleus of our patient may be disease-related. Leptomeningeal thickening due to neuronal accumulation of sphingolipids and cholesterol may cause this perivascular space enlargement and ultimately neuronal death and gliosis.

Although some genetic mutations have been associated with worse metabolic and clinical phenotypes, a wide genetic variability exists, and even in monozygotic twins distinct phenotypes were described [9]. Features seen in infantile-onset cases such as jaundice, hepatosplenomegaly, "gelastic" cataplexy and seizures are less frequent in later-onset cases, while over 25% can initially manifest with psychiatric symptoms.

As a result, it is thought that NPC may be under-diagnosed, particularly in adult-onset cases where it can resemble more common neurodegenerative disorders [5,10].

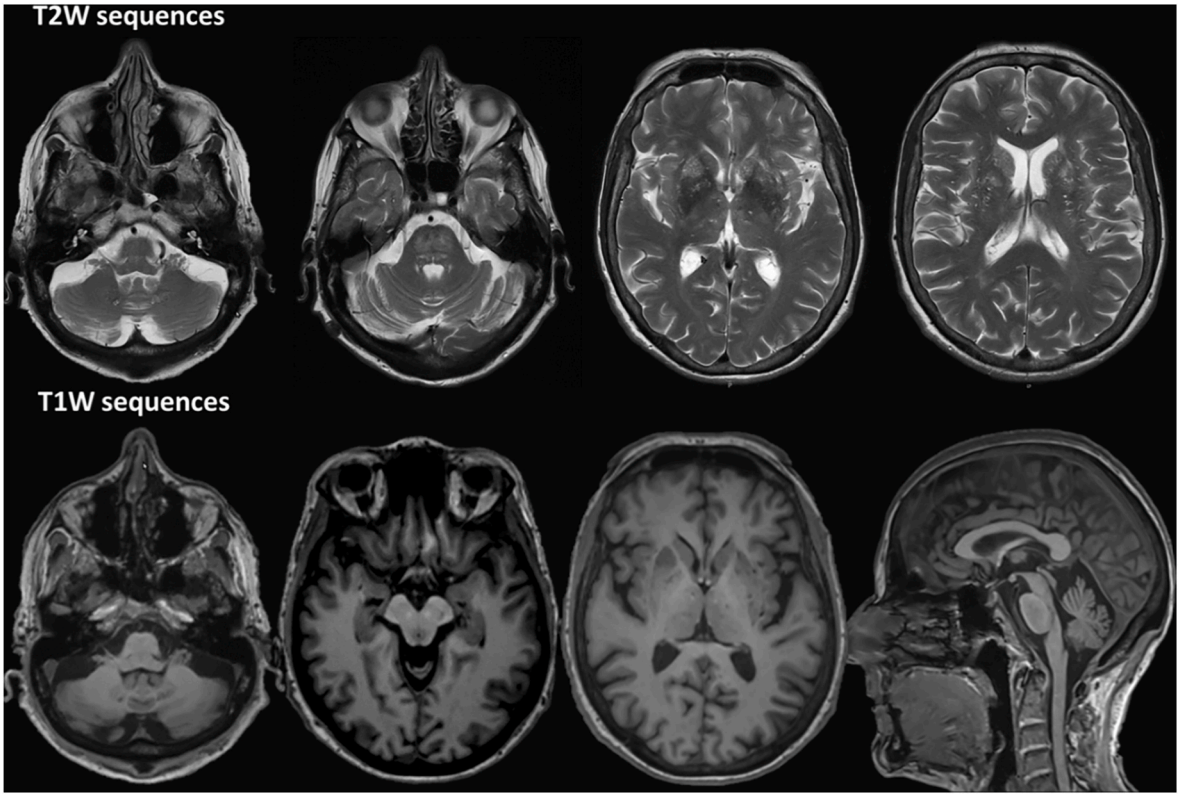

Fig. 1. Brain MRI showing multiple small lesions with hypersignal in T2 weighted images (T2W) with small spotty lesions and cribriform changes suggestive of enlarged perivascular (Virchow-Robin) spaces in the dentate nucleus, globus pallidus and caudate nucleus. In the Pons, there were additional white matter lesions with hypersignal in T2 and variable appearance on T1 weighted images (T1W). There were no clear findings compatible with Hummingbird sign (typically seen in PSP), hot cross bun or putaminal rim signs (supportive imaging features of multiple system atrophy). Note the midline and hemispheric cerebellar atrophy in the T1-weighted-sequences.

Table 1
Detailed literature review of all patients reported with age of onset of neurological symptoms after the age of 40 (for additional details regarding the search strategy used, please see supplementary material).

Author	Age at onset	Gender	First neurological symptom	Motor Phenomenology	Cognitive/Psychiatric features	Brain imaging findings	Others	Oxysterol levels	Genetic findings & diagnosis
Balázs et al., 2019 [11]	41y	Male	- Hearing loss;	- Parkinsonism with postural instability (not levodopa responsive); - Ataxia; - CBS phenotype; - Dysarthria; - VSGP;	- Dementia (decreased verbal fluency, concretization, mild perseveration); - Orofacial apraxia; - Bálint's syndrome;	Brain MRI: - Mild atrophy	- Hepato-splenomegaly;	- 0.196 ng/mL;	*NPC1* c.2861C > T (S954L) + c.3019C > G (P1007A)
Tomic et al., 2018 [12]	43y	Female	- Hearing loss;	- Parkinsonism (bradykinesia without decrement); - Cerebellar ataxia; - Frequent falls; - Dysarthria; - Dysphagia; - Bilateral ptosis; - VSGP;	- Cognitive decline with changes of personality (lack of criticism) and affection; - Visual and hearing hallucinations with the sense of fear and depression;	Brain MRI: - Mild cortical atrophy; - Periventricular demyelinating lesion (+ frontal lobes) DaTSCAN: - unilateral deficit grade I on the right side;	- Incontinence; - Sensorimotor neuropathy - Glomerulonephritis (unknown etiology)	- Not reported;	*NPC1* c.2861C > T (S954L) + c.3019C > G (P1007A)
Josephs et al., 2003 [16]	46y	Female	- Depression and hypersomnolence;	- Postural instability; - Dysphagia; - Dysarthria; - Ataxia; - Parkinsonism; - VSGP; - Cranio-cervical dystonia; - Stimulus-sensitive myoclonus;	- Mood lability, loquacity, delusions, and hypervigilance; - Auditory hallucinations; - Paranoid, hyper-religious, and obsessive thoughts; - Dementia;	Brain MRI: - Small foci of increased T2 signal changes within pons and cerebral white matter;	- Not reported;	- Not reported;	No genetic test performed. Positive Filipin staining test in skin fibroblasts.
Terbeek et al., 2017 [13]	48y	Female	- Balance problems;	- Cerebellar ataxia; - Parkinsonism (bradykinesia without decrement); - Postural instability; - Hyperreflexia; - Dysarthria; - Dysphagia; - VSGP;	- Cognitive impairment; - Pseudobulbar affect;	Brain MRI: - Mild to moderate cerebral and cerebellar atrophy; DaTSCAN: - marked symmetrical loss of dopamine transporter binding (+putamen)	- Sensorineural hearing loss (since childhood) - Mild splenomegaly;	- Not reported;	*NPC1* c.2861C > T, (S954L) + c.3019C > G, (P1007A)
Kumar et al., 2016 [14]	50y	Male	- Hearing loss;	- Ataxia; - Myoclonus (trunk and upper extremities); - VSGP;	- Normal cognition;	Brain MRI: - Cortical and midbrain atrophy with subcortical nonspecific white matter changes;	- Not reported	- Not reported;	*NPC1* c.3019C > G (P1007A) + c.3230G > A (R1077Q)
McFarlane et al., 1988 [17]	51y	Male	- Clumsiness and unsteadiness;	- Cerebellar ataxia; - Dysarthria; - VSGP; - Rigidity;	- Not reported	Brain CT: - cerebral atrophy;	- Pallor of right optic disc; - Sensitive neuropathy; - Positive glabellar tap;	- Not reported	No genetic test performed. Autopsy confirmed case.
Trendelenburg et al., 2006 [15]	54y	Female	- Cognitive impairment; and depression	- Dysphagia; - Cramped hands; - Dyskinesia; - Blepharospasm; - VSGP; - Dystonia; - Anarthria; - Pyramidal signs;	- Depression and fluctuating mood; - Dementia with reduced impulse and affective instability;	Brain MRI: - Mild cerebellar atrophy; - Periventricular signal intensities in the T2/TIRM; Brain FDG-PET: - Bilateral hypometabolism in thalamic and parietooccipital cortical regions;	- Increased CSF protein (73.7 mg/dl); - Mild splenomegaly (14 cm);	- Not reported;	*NPC1* K1206fs + no other mutation identified at that time in the other allele. Positive Filipin staining test in skin fibroblasts.

Abbreviations: VSGP - Vertical Supranuclear Gaze Palsy; y – years.

Authors roles

M.S.: Research project, Conception, Research project, Organization, Research project, Execution, Manuscript Preparation Conception, B.M.: Research project, Conception, Research project, Execution, Manuscript Preparation, B, T.B.: Research project, Execution, Manuscript Preparation, Organization, J.M.N.: Research project, Execution, Manuscript Preparation, Organization, R.W.: Research project, Execution, Manuscript Preparation, Organization, D.A.: Research project, Execution, Manuscript Preparation, Organization, D.B.: Research project, Execution, Manuscript Preparation, Organization, G.T.: Research project, Conception, Research project, Organization, Research project, Execution, Manuscript Preparation, Organization.

Ethical compliance statement

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.

The patient gave written informed consent for publication of this clinical report, and also for publication of images and videos. The authors confirm that the approval of an institutional review board was not required for this work.

Declaration of competing interest

No conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2023.105460.

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