Pearls & Oy-sters: Ocular motor apraxia as essential differential diagnosis to supranuclear gaze palsy

Eyes up

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Pearls

- Ocular motor apraxia (OA) is an inability to initiate voluntary saccades in a head-fixed position, while saccades can be initiated by the vestibulo-ocular reflex (indicating dysfunction in the frontal eye fields).
- Supranuclear gaze palsy (SGP) is a decrease in velocity and range of voluntary saccades and pursuit eye movements, which is overcome via the vestibulo-ocular reflex (indicating dysfunction of mesencephalic gaze control centers).
- Ultimately, both OA and SPG lead to an inability to execute voluntary saccades.

Oy-sters

- Loss of voluntary saccade control with preservation of the vestibulo-ocular reflex is common to OA and SGP, thus requiring further differentiation.
- OA differs from SGP by the retained ability to initiate conjugated eye movements by ipsiversive active head turns.

We report a case exemplifying the clinical differentiation between OA and SGP and discuss their relevance for topical diagnosis in neurology.

Case report

A right-handed 49-year-old man was referred to us for diagnostic evaluation with suspected progressive supranuclear palsy (PSP) with predominant parkinsonism[1,2] when he developed impairments of vertical and horizontal eye movement control after a 2-year history of progressive slowing of the left limbs and jerky movements of the left hand. He had no family history of neuropsychiatric diseases. Eighteen months after symptom onset, cerebral MRI had suggested mild right-sided parietal cortical atrophy and normal midbrain size, [^{123}I]-FP-CIT SPECT had revealed right-sided loss of presynaptic striatal dopamine transporter–positive nerve terminals, and [^{123}I]-iodobenzamide SPECT had shown bilateral symmetric reduction of the postsynaptic striatal D2 receptor expressing neurons. A therapeutic trial with 800 mg of levodopa per day had not yielded symptomatic benefit.

Upon admission, the patient was independent in his activities of daily living. He and his wife perceived his cognition, language, speech, and personality as unimpaired. Comprehensive neuropsychological testing was normal. Physical examination showed mild bradykinesia and rigidity with cogwheeling in the left but not in the right limbs (video 1, links.lww.com/WNL/A220). The left arm showed mild stimulus-sensitive myoclonus. Resting, postural, or action tremor were not observed. Gait examination showed reduced left-sided arm swing. Postural stability was normal. Limb or orobuccal apraxia, alien limb phenomena, and cortical sensory

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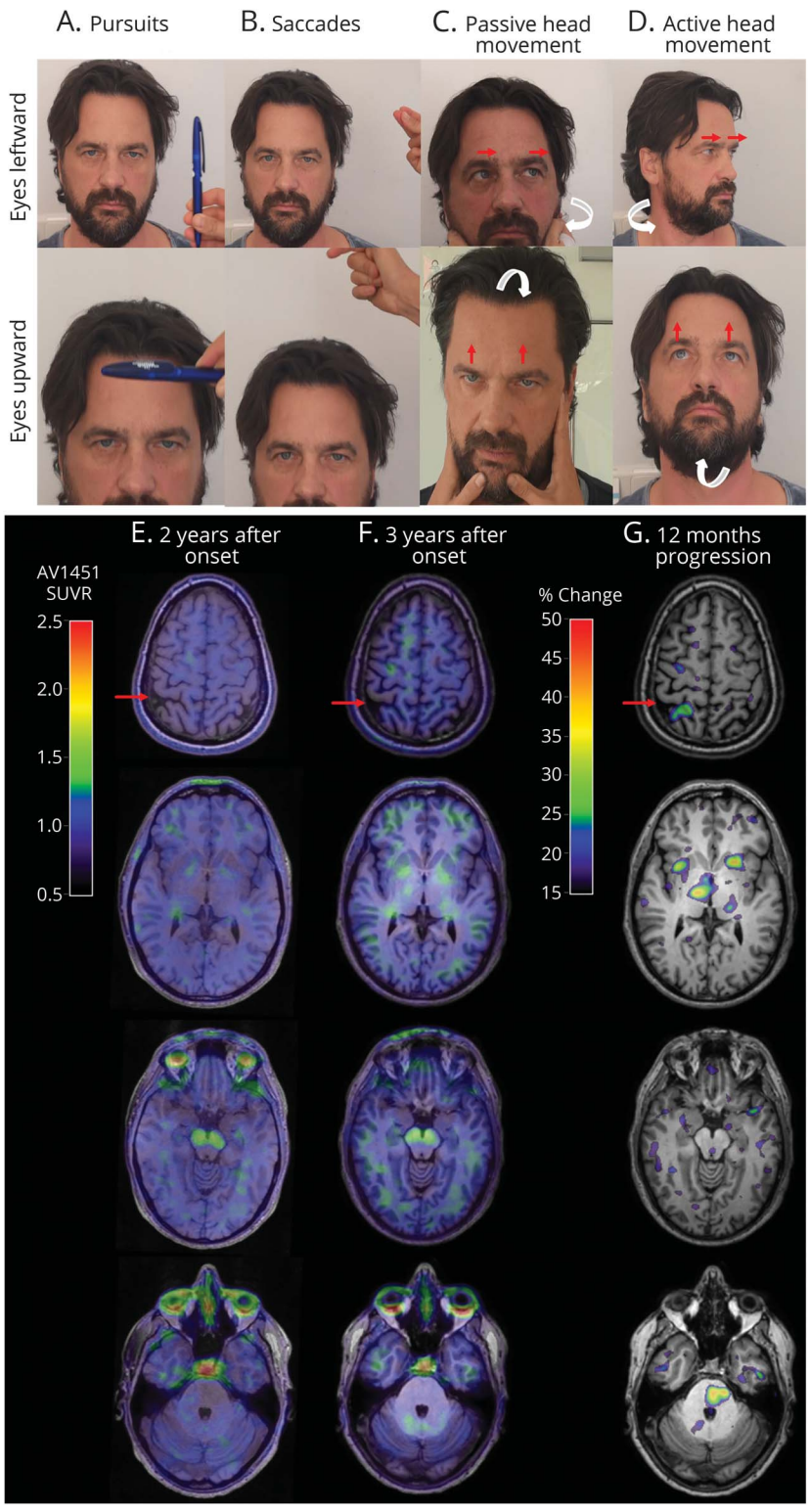
Figure Ocular motor examination and cerebral imaging



The ocular motor examination aimed to elicit voluntary conjugated horizontal (leftward) and vertical (upward) pursuit (A) and saccadic (B) eye movements, as well as reflexive eye movements triggered by passive head turns executed by the examiner (i.e., vestibulo-ocular reflex, C), and by active head movements initiated by the patient (D). This patient was unable to initiate voluntary saccadic or pursuit eye movements in all directions; passive head movements triggered a gaze shift in the contralateral direction showing integrity of the vestibulo-ocular reflex (compatible with a diagnosis of supranuclear gaze palsy [SGP] and ocular motor apraxia [OA]); active head movements initiated a gaze shift in the same direction (compatible with a diagnosis of OA, but not SGP). [^{18}F]-AV-1451 PET superimposed on MRI was obtained 2 years (E) and 3 years (F) after onset of first symptoms (at 47 years of age), and the % change in the PET signal during the 12-month follow-up period (G). The MRI shows the progressive atrophy of the right sided parietal cortex (red arrow). The PET images reveal slightly increased uptake in the right frontal, insular, and parietal cortex. The PET signal increased significantly in the right-sided paracentral region (+40%), insular cortex (+35%), thalamus (+35%), and pallidum (+25%); in the left-sided caudate nucleus (+35%); and centrally in the pons (+35%) and midbrain (+20%).

loss were not present. Examination of the eye movements in a head-fixed position revealed an inability to initiate pursuit movements (figure, A) as well as voluntary or stimulus-evoked saccades (figure, B) in all directions. Eye movements could be triggered by activation of the vestibulo-ocular reflex (reflexive eye movements contralateral to passive head turns; figure, C), suggesting the presence of SGP.[2] However, when the patient actively turned his head or imagined doing so, he

was able to initiate ipsiversive saccades in the direction of the head turn with normal velocity and range (figure, D), demonstrating the presence of OA combined with a reflexive saccade initiation deficit rather than SGP.[3–5]

Several examinations studied possible primary causes of his condition.[2]

All blood laboratory tests were normal, including serum levels of vitamin B_{12} and parathyroid hormone. A paraneoplastic antibody panel was negative. Serum ceruloplasmin and urinary copper excretion were normal, ruling out Wilson disease.

CSF analysis showed normal cell counts, protein levels, and glucose levels, ruling out inflammatory diseases. CSF levels of total tau (136 ng/L, normal <252 ng/L) and S181-phosphorylated tau (26 ng/L, normal <60 ng/L) were normal; β-amyloid (Aβ) 1-42 was slightly decreased (602 ng/L, normal >650 ng/L), but the Aβ 1-42/1-40 ratio was normal (0.081; normal >0.05), ruling out Alzheimer disease (AD).

A diagnostic panel of genes associated with parkinsonism and frontotemporal dementias identified no known mutations in *C9orf72*, *FUS*, *GBA*, *GRN*, *NPC1*, *NPC2*, or *TARDP*. However, the rare p.A152T variant was found in *MAPT*, which has been described as a risk factor for tauopathies.[6,7]

Structural MRI confirmed mild right-sided parietal cortical atrophy (figure, E). PET with the tau-binding tracer [^{18}F]-AV-1451 reported increased signals in AD and non-AD-tauopathies,[8] and revealed slightly elevated uptake in the right-sided frontal, insular, and parietal cortex of our patient (figure, E).

At a follow-up visit 12 months later, the patient reported progression of his symptoms, but was still highly functional in daily life. Neuropsychological testing was still normal. The physical examination now revealed moderate severity of bradykinesia, rigidity, and stimulus-sensitive myoclonus in the left limbs, and a spread of these symptoms in mild severity towards the right limbs. The OA was now noticeable even during normal conversations.

The CSF levels of the AD biomarkers had not changed significantly; total tau (147 ng/L, normal <252 ng/L) and S181-phosphorylated tau (26 ng/L, normal <60 ng/L) were still normal, the level of Aβ 1-42 was slightly more decreased (482 ng/L, normal >650 ng/L), and the Aβ 1-42/1-40 ratio was still in the normal range (0.082; normal >0.05).

Follow-up MRI showed marked progression of the right-sided parietal atrophy and mild right-sided frontal atrophy (figure, F). The follow-up [^{18}F]-AV-1451 PET revealed a similar overall pattern (figure, F), with a substantial increase in signal intensity vs the baseline scan (figure, G) in the right paracentral region (+40%), insular cortex (+35%), thalamus (+35%), and pallidum (+25%); in the left caudate nucleus (+35%); and centrally in pons (+35%) and midbrain (+20%).

Discussion

The prominent ocular motor disorder of the patient was initially suspected to be SGP, suggesting a diagnosis of PSP.[1,2] He was unable to elicit voluntary pursuit movements and saccades in all directions in a stationary head position, while this deficit could be overcome by activation of the vestibulo-ocular reflex during passive head movements. This finding would indeed qualify for SGP according to the standard definition of the term.[2] However, the normal velocity of saccades triggered by active head movements was incompatible with SGP, since a decrease in saccade velocity is highly characteristic for and preceding the onset of SGP in PSP. The patient's ability to trigger conjugated eye movement by imagination or initiation of head movement allowed us to classify his ocular motor deficit as OA.[3–5]

OA can occur in inherited diseases, e.g., in congenital ataxia with OA and in ataxia teleangiectasia.[3–5] Acquired variants are described in strokes affecting the posterior cerebral hemisphere and the posterior part of the frontal lobe including the frontal eye field, in posterior cortical atrophy, and in corticobasal syndrome (CBS).[4,5] Pathophysiologically, the initiation deficit of intentional saccades points to a lesion of the frontal eye fields.[5] The patient's inability to initiative reflexive saccades is uncommon for OA in the strict sense and indicates a more extensive lesion involving also the parietal eye field.[5]

MRI and PET confirmed atrophy and increased [^{18}F]-AV-1451 signal intensity in the frontal and parietal eye fields with right-sided predominance. A lateralization of eye movement control has been described in humans, with a higher degree of saccadic abnormalities in right-sided cortical lesions.[9]

The combination of the basal ganglionic signs (rigidity, akinesia, and myoclonus) with the cortical sign (OA) in absence of postural instability and cognitive and behavioral deficits was best classified as CBS.[2,10] The asymmetric parietal cortical atrophy without mesencephalic atrophy on MRI, along with the presynaptic and postsynaptic nigrostriatal dopaminergic degeneration on SPECT, provided structural support to this diagnostic classification.

In clinically diagnosed CBS, the most frequent neuropathologic diagnoses are corticobasal degeneration (CBD), PSP, or AD (25%–30% each).[10] In our patient, the normal CSF tau concentration and Aβ 1-42/1-40 ratio virtually ruled out AD. The identified p.A152T *MAPT* variant predisposes for tauopathies, including PSP and CBD, associated with a CSF biomarker pattern as in our patient.[6,7] Consistently, [^{18}F]-AV-1451 PET suggested tau pathology with the highest 12-month progression rate in the right-sided parietal and insular cortex, and bilaterally in the striatum. This asymmetric corticobasal ganglionic pattern is most likely caused by CBD pathology, but PSP pathology also can cause such a pattern and cannot be

ruled out with certainty in our patient.[2,10] Therefore, we diagnosed this patient with clinical CBS with probable underlying 4R tauopathy (i.e., a primary tauopathy with predominant aggregation of tau isoforms with 4 microtubule-binding sites).[1,2]

This case demonstrates the relevance of considering OA as clinical clue for the diagnosis of CBS. OA points to a dysfunction in the area of the frontal eye fields (voluntary saccade initiation).[5] Additional dysfunction in the parietal eye fields may eventually impair initiation of reflexive saccades, as in our patient.[5] In contrast, SGP originates from dysfunction of supranuclear centers of gaze control (i.e., the interstitial nucleus of Cajal and rostral interstitial nucleus of the medial longitudinal fasciculus in the midbrain, and the paramedian pontine reticular formation).[5] The cortical predominance of neurodegeneration was demonstrated in our patient by MRI and [^{18}F]-AV-1451 PET, neither of which showed mesencephalic pathology. Our patient's case was particularly challenging, since OA was present in absence of limb or orobuccal apraxia, which are the more frequently observed manifestations of apraxia in CBS.[2,10]

For clinical practice, OA can be differentiated at bedside from SGP by testing the patient's ability to initiate conjugated eye movements by voluntary ipsiversive active head turns (present only in OA) as opposed to vestibular reflexive eye movements contraversive to passive head turns (present in both OA and SGP).

Author contributions

Kerstin Schweyer: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript. Marc Aurel Busche: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content. Jochen Hammes: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content. Andreas Zwergal: analysis and interpretation of data, critical revision of the manuscript for intellectual content. Carsten Buhmann: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content. Thilo van Eimeren: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content. Günter U. Höglinger: study concept and design, acquisition of data, analysis and interpretation of data, study supervision, drafting the manuscript for intellectual content.

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Disclosure

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