

Nicolas Vandenbussche,  
MD  
Catherine Cassiman, MD  
Maarten Schrooten, MD  
Benjamin Gille, Msc  
Xavier Bossuyt, MD, PhD  
Thierry Vincent, MD,  
PhD  
Philip Van Damme, MD,  
PhD  
Koen Poesen, PharmD,  
PhD

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## NEGATIVE COMMERCIAL SCREENING TEST FOR PARANEOPLASTIC ANTIBODIES IN A CASE OF OPSOCLONUS

### OPEN

The diagnosis of a paraneoplastic syndrome (PNS) is challenging as it comprises a group of clinically heterogeneous entities, all related to a coexistent, but sometimes occult, malignancy.<sup>1</sup> The detection of paraneoplastic antibodies aids the clinician to establish the diagnosis of a PNS.<sup>2</sup> Paraneoplastic antibodies are screened for by means of immunohistochemistry or indirect immunofluorescence on cerebellar slices.<sup>2</sup> Cerebellar substrates that can be used for screening for paraneoplastic antibodies are commercially available.<sup>3</sup>

Such commercial screening was applied to screen the serum and CSF of a 48-year-old woman presenting with a subacute onset of oscillopsia and diplopia. No family history of neurologic diseases was present. Two months before, she experienced the initial symptoms of anorexia, nausea, and balancing problems. Two weeks before admission, she experienced the first signs of multidirectional binocular diplopia and oscillopsia. Neurologic examination revealed a normal mental and cognitive status. Ocular motility showed full-range eye movements. The patient mentioned binocular diplopia on lateral gaze and downgaze. Initially, bursts of ocular flutter were noticed, confirmed by video-oculography, which evolved over time into a constant opsoclonus. This opsoclonus caused significant visual impairment with a drop of visual acuity to logMAR 0.7. She had a normal motor and sensory examination. The osteotendinous reflexes were brisk without pathologic reflexes. Gait was broad-based ataxic, without overt appendicular ataxia. In a later phase, she mentioned infrequent shock-like movements of arms and head, reminiscent of myoclonus. Logopedic examination revealed prolonged oral processing with delayed initiation of swallowing and incomplete elevation of the larynx, without further objective abnormalities during deglutition. CT and MRI of the brain and brainstem and peripheral otovestibular tests revealed no abnormalities.

An autoimmune screening was negative in the serum (table). The positive findings of an extensive biochemical, microbiological, and cytologic examination of the CSF are presented in the table. Initial

screening for paraneoplastic antibodies on admission and the next day was negative in the serum and in the CSF (table). Negativity was independently confirmed using the same commercial assay (table). Serum tests for anti-NMDA receptor antibody, anti-voltage-gated calcium channels antibody, anti-ganglioside/sulfatide antibodies, and anti-glutamic acid decarboxylase I/II antibody were negative as well.

A 2-[<sup>18</sup>F] fluoro-2-deoxy-D-glucose PET confirmed a suspicious mammography, revealing a strong hypermetabolic region in the right breast, without further evidence of hypermetabolic lymph nodes or distant metastasis. Histologic examination of a broadly excised breast tumor section showed a grade 2 moderately differentiated invasive ductal adenocarcinoma and 3 negative sentinel nodes. A seronegative PNS with ocular opsoclonus and gait ataxia was diagnosed. Oral methylprednisolone and IV plasmapheresis had no significant effect.<sup>1</sup> Clonazepam and gabapentin relieved some of the oscillopsia. Tamoxifen was started 2 weeks after surgery. Adjuvant radiotherapy (daily fractions of 2.66 Gy to a total dose of 42.56 Gy) and chemotherapy, consisting of 4 cycles of epirubicin and cyclophosphamide followed by 12 cycles of Taxotere, was started 7 and 13 weeks after surgery, respectively. Opsoclonus completely disappeared, and hence visual acuity improved accordingly (logMAR 0.1). Gait ataxia improved significantly, allowing her to walk without walking aids again.

Given the negative test results for antibodies contrasting with a clear PNS, the serum and the CSF samples taken at admission were reassessed for paraneoplastic antibodies by a noncommercial immunohistochemical screening using rat brain tissue.<sup>2</sup> This screening suggested the presence of anti-Ri antibodies (table). The latter was confirmed using an immunoblot of recombinant protein similar to the one published before<sup>2</sup> and a commercial immunodot assay as well (table).

Here, we report that a commercial screening for paraneoplastic antibodies, which is applied worldwide,<sup>3</sup> failed to detect anti-Ri antibody in the serum and in the CSF of a patient with a PNS. Only one relatively small study addressed the sensitivity of a commercial screening test before, and that results were positive in 2/2 Ri, 6/6 Hu, 3/5 Yo, and 0/2 Ma2

**Table Serum and CSF results of interest for the case**

	Assay	Result	Cutoff
<b>Screening for paraneoplastic antibodies (serum and CSF)</b>			
Initial screening	IIF on monkey cerebellum (Inova Diagnostics, San Diego, CA)	Absent (confirmed on the second serum sample)	
Independent confirmation (CHRU Montpellier, France)	IIF on monkey cerebellum (Inova Diagnostics)	Absent	
Hospital Clinic, University of Barcelona, Spain <sup>2</sup>	IHC on rat brain tissue <sup>2</sup>	Pattern suggestive of anti-Ri antibody	
<b>Typing of paraneoplastic antibodies in the serum and CSF</b>			
Hospital Clinic, University of Barcelona, Spain <sup>2</sup>	Recombinant immunoblot <sup>2</sup>	Anti-Ri antibody	
CHRU Montpellier, France	Immunodot (Ravo Diagnostika, Freiburg, Germany)	Anti-Ri antibody	
CSF cytosis	Manual cytology (May-Grünwald-Giemsa staining)	8.2 cells/ $\mu$ L lymphocytic formula	<5/ $\mu$ L
IgG index	Nephelometry (Beckman Coulter, Brea, CA)	0.63	0.30-0.60
IgG synthesis	Hydragel CSF isofocussing (Sebia, Lisses, France)	12 intrathecal oligoclonal bands exclusively in CSF	

Abbreviations: IIF = indirect immunofluorescence; IHC = immunohistochemistry.

patients' serum, without, unlike our case, any CSF antibodies status available.<sup>3</sup> A screening for the sake of cost-efficiency requires a high sensitivity to avoid false-negative results as the presence of a paraneoplastic antibody directs the clinician toward the diagnosis of a PNS, especially in clinically doubtful cases.<sup>4</sup> Providing clinical information along with the laboratory request enables the clinical pathologist to direct testing as proposed by international guidelines, which might avoid false-negative results when clinical suspicion is high.<sup>4</sup> Our case illustrates that screening for paraneoplastic antibodies by commercially available tissue-based assay might miss individual cases that are detected by other methods.<sup>5</sup>

*From the Department of Neurology (N.V., M.S., P.V.D.), Department of Ophthalmology (C.C.), and Laboratory Medicine (X.B., K.P.), University Hospital Leuven; Department of Microbiology and Immunology (X.B.), Experimental Laboratory Immunology, Leuven, Belgium; Department of Immunology (T.V.), St Eloi Hospital, Montpellier University, France; Department of Neurosciences (P.V.D.), Laboratory for Neurobiology; Vesalius Research Center (P.V.D.), Flemish Institute for Biotechnology (VIB); and Department of Neurosciences (B.G., K.P.), Laboratory for Molecular Neurobiomarker Research, Leuven, Belgium.*

*Author contributions: Nicolas Vandenbussche: sample collection, design and conceptualization of the study, data generation, data interpretation, and drafting of the manuscript. Catherine Cassiman: design and conceptualization of the study, data generation, data interpretation, and revising the manuscript for intellectual content. Maarten Schrooten: sample collection, data generation, data interpretation, and revising the manuscript for intellectual content. Benjamin Gille: sample collection and revising the manuscript for intellectual content. Xavier Bossuyt and Thierry Vincent: data generation, data interpretation, and revising the manuscript for intellectual content. Philip Van Damme: sample collection, design and conceptualization of the study, data generation, data interpretation, and revising the manuscript for intellectual content. Koen Poesen: design and conceptualization of the study, data generation, data interpretation, and drafting of the manuscript.*

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*Correspondence to Dr. Poesen: [koen.poesen@uzleuven.be](mailto:koen.poesen@uzleuven.be)*

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