Sleep disorder associated with antibodies to IgLON5: parasomnia or agrypnia?

We read with great interest the paper by Lidia Sabater and colleagues,[1] who describe a novel neuroimmunological disease that is a complex, severe sleep disorder associated with antibodies to IgLON5. We have noted a clinically similar disorder in a single patient who had serum and CSF antibodies to the metabotropic $GABA_B$ receptor.[2,3] Similar to the patients in Sabater and colleagues' report, our patient developed a complex neurological syndrome at age 55 years that was characterised by diplopia, slight fluctuating bilateral palpebral ptosis, and, later, dysphagia, dysphonia, tongue weakness, stridor, severe dysautonomia, and central hypoventilation, which required assisted ventilation during sleep. The outcome was also similar to the outcomes reported by Sabater and colleagues.[1] Despite long periods of amelioration after plasma exchange and immunosuppressive treatment, the patient died suddenly during sleep 10 years after the onset of the disease. Sleep recordings showed a period of complete sleep loss in the acute phases of the disease.

Agrypnia has been associated with neuroimmunological disorders, and particularly with Morvan's chorea. Essentially, it is a complete loss of sleep, with the elimination of slow-wave sleep and sleep spindles that are associated with sustained motor and autonomic activation. We believe that this peculiar sleep disorder described by Sabater and colleagues has several features in common with the syndrome described by Lugaresi and colleagues[4] as agrypnia excitata: the presence of undifferentiated non-rapid-eye movement sleep stages; the absence of the rapid-eye-movement atonia; the dysautonomia disorder; and the continuous motor activity during sleep. The finalistic movements described in Sabater and colleagues' paper might be interpreted as episodes of oneiric stupor, which is probably an exclusive sign of agrypnia excitata and it is the recurrence of stereotyped gestures mimicking simple daily life activities.[5] However, the patients had some episodes of N3 stage sleep, preserved K complexes slow-wave sleep, and spindles, which are not the typical findings in agrypnia excitata. Nevertheless, in all disorders associated with agrypnia excitata, spindles, K complexes, and slow-wave sleep show a progressive reduction before disappearing. In our patient and other cases of agrypnia in our clinical experience, the sleep pattern and the other neurological symptoms had a relapsing-remitting course. In sleep recordings done serially and prolonged for several consecutive days, slow-wave sleep and spindles presented alternated periods of total suppression with periods of partial reduction, associated with the clinical fluctuation.

Therefore, we suggest that the disorder elegantly described by Sabater and colleagues,[1] which was associated with anti-IgLON5 autoantibodies, could be regarded as a type of agrypnia excitata rather than as a parasomnia, similar to that seen in other neuroimmunological diseases.

We declare no competing interests.

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Authors' reply

We thank Giacomo Della Marca and colleagues for their interest in our report.[1] In their view, the sleep disorder of patients with IgLON5 antibodies has many similarities to agrypnia excitata, particularly the presence of undifferentiated non-rapid-eye movement sleep, rapid-eye movement sleep without atonia, and finalistic behaviours such as those described in fatal familial insomnia. As indicated in our report, patients with IgLON5 antibodies do not have agrypnia (a complete absence of sleep). Our patients had the characteristic presence of well identified periods of stage N3 with sleep spindles that are atypical for agrypnia excitata. Despite this, Della Marca and colleagues suggest that sleep spindles, K complexes, and delta slowing would have eventually disappeared with prolonged follow-up. This speculation, however, does not apply to our patients. In patients 1–3, we recorded 15 sleep studies throughout 4 years and the sleep abnormalities did not show substantial progression. Additionally, patients 5 and 7 had a sleep study recorded a few weeks before death, and periods of delta slowing and sleep spindles were clearly present. In our view, the sleep disorder in patients with IgLON5 antibodies is best described as a parasomnia involving non-rapid-eye movement and rapid-eye movement sleep, with normal N3 sleep periods during parts of the night, and sleep breathing disorder with stridor. This combination of elements is novel, and has not been described in fatal familial insomnia, Morvan's syndrome, or delirium tremens—the three best examples of agrypnia excitata. We

think that the complexity of the sleep changes requires a detailed description of their elements for an improved understanding of the pathophysiological mechanisms and anatomical substrate rather than forcing the disorder into a particular category.

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Complexity of the endovascular intervention and clinical outcomes in acute ischaemic stroke

We were particularly interested in the paper by Khatri and colleagues on time to angiographic reperfusion and clinical outcome after acute ischaemic stroke in the Interventional Management of Stroke phase 3 trial (IMS III).[1] We obtained similar results (the odds ratio of favourable outcome [modified Rankin scale 0–1] was significantly decreased by the delay of endovascular treatment conclusion) in the SYNTHESIS Expansion trial,[2] the findings of which were presented at the European Stroke Conference (May 6–9, 2014)[3] but have not yet been submitted for publication. We offer an alternative explanation for the link between time to reperfusion and clinical outcome. Indeed, the effect of time to treatment on outcome in the study of Khatri and colleagues[1], as we experienced in the SYNTHESIS Expansion trial, was statistically significant when assessed from stroke onset to the end of treatment—"time to angiographic reperfusion was defined as the time from stroke onset to termination of the endovascular treatment procedure" —but not when assessed from stroke onset to the start of treatment. Therefore, the chance of good clinical outcome depends on the duration of treatment rather than on the delay to treatment initiation. The duration of endovascular treatment might depend on many factors, such as difficulty in peripheral arterial access or in reaching the occlusion site, the patient's movements, the necessity of anaesthesia and intubation, the patient's vascular architecture, and the degree of collateralisation and a number of features of the occlusion (thrombus location, the presence of flow within the proximal vascular segment, and length and composition of the thrombus).[4] Therefore, the complexity of the intervention could be one reason for the delay to procedure termination (ie, opening of the vessel is more difficult, and so the intervention is longer). When interpreted in this way, the finding that delay to angiographic reperfusion leads to a decreased likelihood of good clinical outcome could depend on the complexity of the intervention rather than on time itself. Even though the finding of a time-to-reperfusion effect in the endovascular treatment group of IMS III[1] is straightforward and of clinical relevance to clinicians, this result would have been more convincing if the delay to endovascular procedure initiation, and not only to angiographic reperfusion, had been associated with a decreased likelihood of good clinical outcome. We think that our alternative interpretation should be considered in the planning of future clinical trials, since time might not be the overriding factor in explaining the lack of superiority of endovascular treatment over intravenous thrombolysis in the IMS III[1] and the SYNTHESIS Expansion[2] trials.

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Authors' reply

We thank Ciccone and the SYNTHESIS trialists for their important and thoughtful inquiry and the opportunity to clarify our findings.

We cautiously considered alternative explanations for our observation that time from symptom onset to angiographic reperfusion (defined by the end of the endovascular procedure) predicted clinical outcome after ischaemic stroke in the Interventional Management of Stroke (IMS) III trial. In particular, we did indeed consider the possibility