Opsoclonus-Myoclonus Syndrome in Patients With Locked-in Syndrome: A Therapeutic Porthole With Gabapentin

FRANCESCA PISTOIA, MD; MASSIMILIANO CONSON, PhD; AND MARCO SARÀ, MD

Patients with locked-in syndrome, although fully conscious, have quadriplegia, mutism, and lower cranial nerve paralysis. The preservation of vertical gaze and upper eyelid movements usually enables them to interact with the environment through an eye-coded communication. However, locked-in syndrome may be complicated by the development of an opsoclonus-myoclonus syndrome that may represent an additional impediment to communication. We evaluated whether off-label treatment with gabapentin could help patients with locked-in syndrome and opsoclonus-myoclonus symptoms regain voluntary control of full eye movements. A mechanism responsible for gabapentin-induced improvement has been also hypothesized. In this study, 4 patients presenting with locked-in syndrome complicated by opsoclonus-myoclonus syndrome were continuously treated with gabapentin up to 1200 mg/d. The treatment resulted in a rapid and long-lasting resolution of opsoclonus-myoclonus symptoms without adverse effects. After 2 weeks, patients showed voluntary attempts to communicate through eye blinking and thereafter regained voluntary control of full eye movements. This event enabled them to regain a communication channel with relatives and physicians and to start using eye-controlled brain-computer interfaces. Because of its effectiveness in restoring eye movement control, gabapentin opened a communicative porthole in the patients' lives. Since opsoclonus may be related to disorders of the inhibitory control of saccadic burst neurons by pontine pause cells, we hypothesize that gabapentin acts as a regulator of saccadic circuits.

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Sight and hearing were the only senses remaining....It was only, however, by means of one of these senses that he could reveal the thoughts and feelings that still occupied his mind, and the look by which he gave expression to his inner life was like the distant gleam of a candle which a traveller sees by night across some desert place, and knows that a living being dwells beyond the silence and obscurity. In his eyes, shaded by thick black lashes, was concentrated, as it often happens with an organ which is used to the exclusion of the others, all the activity, address, force, and intelligence which were formerly diffused over his whole body; and so although the movement of the arm, the sound of the voice, and the agility of the body, were wanting, the speaking eye sufficed for all.

In this brilliant way, Alexandre Dumas¹ described locked-in syndrome in *The Count of Monte Cristo* before the scientific community acknowledged it as a well-codified clinical syndrome. Locked-in syndrome is a neurologic condition characterized by preserved consciousness, quadriplegia, mutism, lower cranial nerve paralysis, and preservation of vertical gaze and upper eyelid movement.² Most cases are caused by a ventral pontine infarction that is responsible for the disruption of the brainstem's cortico-

spinal, corticobulbar, and corticofacial pathways. Patients with locked-in syndrome interact with their environment by means of eye-coded communication strategies: they usually look up or blink once to say yes and look down or blink twice to say no. Indeed, they are usually able to spell entire words by selecting letters on a letter board.

However, some patients with locked-in syndrome may be betrayed by their eyes as a consequence of the appearance of opsoclonus-myoclonus symptoms. Eye movement disorders cause an extreme motor imprisonment that further reduces patients' communication tools. We previously described improvement in one patient after treating ocular movement disorders with gabapentin.³ The aims of this article are to summarize our recent findings on an extended group of patients treated with gabapentin and to speculate on the mechanisms responsible for the observed improvement.

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REPORT OF CASES

Of 10 patients with locked-in syndrome admitted to our Post-Coma and Rehabilitation Care Unit within a 6-month period, 4 developed opsoclonus-myoclonus symptoms, thus experiencing severe difficulties in eye-coded communication strategies. Demographic and clinical characteristics of these patients are reported in the Table.

Locked-in syndrome was the consequence of a pontine infarction after a basilar artery thrombosis in 2 cases (patients 1 and 2). It was the result of a pontine hemorrhage from a brainstem cavernous malformation and of central pontine myelinolysis in the remaining cases (patients 3 and 4, respectively). The brainstem lesions for each patient are shown in Figure 1.

In the acute phase, patients experienced a consciousness impairment with respiratory failure, thus requiring trache-

From the Post-Coma Intensive and Rehabilitation Care Unit, Hospital San Raffaele, Cassino, Italy (F.P., M.S.); Department of Internal Medicine and Public Health, University of L'Aquila, L'Aquila, Italy (F.P.); and Neuropsychology Laboratory, Department of Psychology, Second University of Naples, Naples, Italy (M.C.)

Individual reprints of this article are not available. Address correspondence to Francesca Pistoia, MD, Hospital San Raffaele, via Gaetano di Biasio 1, 03043 Cassino (FR), Italy (pistoiafrancesca@hotmail.com).

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TABLE. Demographic and Clinical Characteristics of the Study Patients

Patient No./sex/ age (y)	Cause of LIS	Disease duration (mo)	Time to develop OMS (mo)	Gabapentin dose (mg)	Length of treatment (mo)
1/M/56	Pontine infarction after basilar artery thrombosis	6	2	1200	6
2/M/66	Pontine infarction after basilar artery thrombosis	9	5	600	5
3/F/58	Pontine hemorrhage from cavernous angioma	13	2	600	7
4/M/65	Central pontine myelinolysis	5	4	1200	5

LIS = locked-in syndrome; OMS = opsoclonus-myoclonus syndrome.

ostomy and invasive mechanical ventilation. At admission to our unit, patients were fully conscious, breathing spontaneously, and fed by percutaneous endoscopic gastrostomy. They showed a complete locked-in syndrome characterized by tetraparesis, mutism, lower cranial nerve paralysis, and preservation of vertical gaze and upper eyelid movement. Early attempts to communicate by eye blinking and vertical eye movements were encouraged. Patients learned to communicate by means of eye-coded strategies; these move-

ments were progressively reinforced, thus enabling patients to respond to closed questions (yes/no) and to spell entire words and sentences by selecting letters on a letter board. However, after some months, patients began to show a rapid twitch of their eyes that partially impaired their vision and communication code. Ocular movement disorders progressively worsened, leading to the development of a classic opsoclonus-myoclonus syndrome, which developed at variable times after the pontine insult, ranging from 2 to 5 months.

FIGURE 1. Brain magnetic resonance images for patients 1 and 2 showing the pontine ischemic lesion (A and B) and for patient 3 showing the pontine hemorrhage (C). Computed tomogram for patient 4 showing the central pontine myelinolysis (D).

FIGURE 2. Physical Component Summary (PCS) and Mental Component Summary (MCS) scores for each patient as obtained by the 36-Item Short Form Health Survey. Locked-in syndrome was affected more on the PCS than on the MCS.

As a consequence, patients experienced both perceptive and communicative difficulties: they were unable to hold their gaze on specific directions, with repercussions on their abilities to explore the environment. Moreover, any communication with other people was completely precluded. On the basis of a previous successful experience, daily continuous treatment with gabapentin was started. The severity of the opsoclonus-myoclonus syndrome and the benefits obtained with gabapentin were assessed through repeated clinical examinations. Moreover, during resting electroencephalographic recordings, an electrooculogram (0.3- to 70-Hz bandpass) was also collected to monitor eye movements and quantify the presence of ocular and blinking artifacts and its reduction over time. For all patients, therapy was initiated as a single 300-mg dose on day 1 followed by 600 mg/d in divided doses on day 2. This dose was enough to consistently reduce ocular symptoms in patients 2 and 3 with a following improvement in communication and quality of life. The dose was further increased in the remaining patients, with the best response being observed by reaching a daily 1200-mg dose. In all patients, several attempts to discontinue the treatment resulted in the reappearance of opsoclonus-myoclonus that recurred approximately 6 hours after the last dose. Therefore, the treatment was promptly resumed.

Patients are currently taking gabapentin with no adverse effects; main adverse effects, such as dizziness, somnolence, and xerostomia, were excluded by directly asking patients as soon as a functional communication was established. Peripheral edema was excluded through repeated physical examinations, whereas ataxia was hard to recog-

nize because patients persistently showed an extreme motor disability with severe tetraparesis.

Because of gabapentin-induced improvement, patients regained a satisfying quality of life. Because a communication channel was established, the 36-Item Short Form Health Survey was administered to assess the physical and mental health of the patients.⁴ As endorsed by the Physical Component Summary and Mental Component Summary for each patient (Figure 2), the impact of locked-in syndrome appeared much larger on the Physical Component Summary than on the Mental Component Summary, the latter being similar to that found in the general population or in patients with a milder disability.

DISCUSSION

Gabapentin, by reducing the opsoclonus-myoclonus symptoms, opened a communicative porthole for patients and greatly improved their quality of life. The opsoclonus-myoclonus syndrome or dancing eye syndrome is characterized by combined horizontal, vertical, and/or torsional, disconjugate saccadic oscillations (saccadomania). Eyes spontaneously and continuously oscillate in a variety of directions beyond patients' control. Moreover, opsoclonus is frequently associated with an hyperexcitable blink reflex favoring the emergence of myoclonus.^{5,6}

Opsoclonus-myoclonus symptoms may sometimes occur in patients with brainstem lesions, together with palatal tremor, orofacial stereotypes, and abnormal posturing movements.⁷ As a consequence of the brainstem lesion, patients with locked-in syndrome may occasionally show

opsoclonus-myoclonus symptoms that further contribute to their disability and functional communication impairment. Currently, no clear information is available on the frequency of opsoclonus-myoclonus symptoms in patients with locked-in syndrome, probably because of the absence of larger-scale controlled studies. The most extensive study reported involuntary motor phenomena in 50 of 139 patients; ocular bobbing was the most frequently reported phenomenon.⁸ Our study also suggests that involuntary ocular movements might be more frequent than expected; although our sample might not be representative of the whole population of locked-in patients, an underestimation of opsoclonus-myoclonus symptoms cannot be excluded. Further systematic studies are needed to explore the true prevalence of this syndrome after pontine lesions. This is even more necessary if we consider that missed opportunities in establishing a communication code with these patients might contribute to a high rate of misdiagnoses, which may not be corrected for a long time.⁹

Clear medical protocols to treat opsoclonus-myoclonus symptoms are not currently available. Corticotropin, high-dose immunoglobulin, or methylprednisolone has been suggested for the treatment of symptoms of paraneoplastic origin, with therapeutic choices being limited by the high toxicity and the high number of adverse effects associated with these treatments.¹⁰ Unsatisfactory results have been described in patients with locked-in syndrome treated with baclofen or clonazepam.⁷

To our knowledge, there is only one piece of evidence in the literature about the therapeutic effectiveness of gabapentin within this field; it refers to the case of a patient with cervical uterine neoplasia and opsoclonus-myoclonus-associated symptoms.¹¹ We recently indicated gabapentin as a potential treatment of ocular movement disorders in a patient with a pontine lesion, without focusing on the mechanism by which gabapentin may exert its effect.³

The current findings confirm the therapeutic usefulness of gabapentin. To date, gabapentin is formally considered as treatment of partial seizures and painful neuropathies. Adverse effects, such as asthenia, diarrhea, peripheral edema, dizziness, and somnolence, are rare and mainly occur with higher doses. Gabapentin is contraindicated in patients who have previously demonstrated hypersensitivity to the drug, and the dose needs to be adjusted downward in patients with renal impairment. Moreover, gabapentin therapy should not be discontinued abruptly after long-term use because of the possibility of increasing seizure frequency in epileptic patients. When these precautions are followed, gabapentin is considered safe treatment.

Because of its long-lasting safety and effectiveness and the lack of serious adverse effects, gabapentin might become the first choice in the treatment of ocular movement disorders,

especially in patients with a severe communicative impairment. Compared with previously proposed treatments, whose administration is limited by high toxicity, gabapentin is more effective and safer. If our results are further confirmed, treatment with gabapentin might be proposed in a meaningful number of patients who, irrespective of their primitive disease (pontine lesion, paraneoplastic syndrome, degenerative disease), show ocular movement disorders.

As with ocular flutter, the possible pathophysiology of opsoclonus may be related to disorders of the inhibitory control of saccadic burst neurons by pontine pause cells.¹² Normal saccadic movements are subserved by tonic neurons, which, in their turn, are modulated by *burst neurons* that are responsible for saccadic eye velocity commands and *pause neurons* that discharge tonically except just before and during saccades, thus exerting a tonic inhibitory influence on saccadic burst neurons. Because of the action of pause neurons, at the end of each saccade the eye is held in its new position against orbital elastic-restoring forces and saccadic intrusions are avoided. The action of burst and pause neurons must be appropriately matched by an integrator network, which is located in the pontine paramedian reticular formation; an unbalance in their mutual action, resulting from a pontine cell dysfunction, may give rise to opsoclonus symptoms (Figure 3). Moreover, there is strong evidence that pause neurons are involved in modulation of trigeminal reflex blinking, whose dysfunction leads to myoclonus symptoms.⁶ Gabapentin might reverse opsoclonus symptoms by acting as a regulator of the saccadic circuit's gain; it might exert its action either by enhancing pause neurons or by inhibiting the burst ones.

Patients with locked-in syndrome classically have a ventral pontine lesion. However, wide pontine damage, which occurs in either severe brainstem infarcts and hemorrhages or central pontine myelinolysis, may cause destruction of the mediodorsal part of the pons, which facilitates the development of opsoclonus-myoclonus syndrome. Typically, opsoclonus-myoclonus syndrome manifests several months after the acute event, probably because of transneuronal degeneration of pontine paramedian reticular formation cells in response to loss and deafferentation of motoneurons. This is endorsed by neuropathologic studies in patients with opsoclonus-myoclonus syndrome, which revealed distinctive abnormalities in the brainstem and cerebellum (lymphocytic infiltration in the neocortex, pons, and cerebellum and loss of Purkinje cells and cerebellar granular layer cells).¹³

CONCLUSION

Ocular movement disorders are observed more than expected in patients with various types of pontine lesions.

FIGURE 3. Neural network that subserves the ipsilateral horizontal conjugate gaze. From the abducens nucleus (VI), both axons that innervate the lateral rectus (LR) and axons that cross the midline arise; the last ascend into the medial longitudinal fasciculus (MLF) and innervate the medial rectus (MR) motoneurons located at the oculomotor nucleus (III). Excitatory burst neurons (EBN) and pause neurons (PN) are located within the pontine paramedian reticular formation (PPRF). Saccadic accuracy is supported by a balance between the EBN and PN and their effect on ipsilateral tonic neurons (TN) and contralateral inhibitory burst neurons (IBN). Full and empty arrows indicate excitatory and inhibitory synapses, respectively.

As a consequence of these disorders, patients experience further frustration because they are unable to communicate and to use eye-controlled brain-computer interfaces, tools that are regarded as being promising in restoring communication for people with severe motor disabilities. Although additional studies are necessary to clarify the exact mechanism underlying the observed improvement, gabapentin shows great potential in restoring normal eye movement control and functional communication in these patients.

REFERENCES

1. Dumas A. *The Count of Monte Cristo*. London, England: Wordworth Editions Limited; 1997.
2. Bauer G, Gerstenbrand F, Rimpl E. Varieties of the locked-in syndrome. *J Neurol*. 1979;221(2):77-91.
3. Pistoia F, Sarà M. Gabapentin therapy for ocular opsoclonus-myoclonus restores eye movement communication in a patient with a locked-in syndrome [published online ahead of print November 20, 2009]. *Neurorehabil Neural Repair*.
4. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36® Health Survey Manual and Interpretation Guide*. Boston, MA: New England Medical Center, The Health Institute; 1993.
5. Hersh B, Dalmau J, Dangond F, Gultekin S, Geller E, Wen PY. Paraneoplastic opsoclonus-myoclonus associated with anti-Hu antibody. *Neurology*. 1994;44(9):1754-1755.
6. Chen FP, Evinger C. Cerebellar modulation of trigeminal reflex blinks: interpositus neurons. *J Neurosci*. 2006;26(41):10569-10576.
7. Tilikete C, Hannoun S, Nighoghossian N, Sappey-Marini D. Oculopalatal tremor and severe late-onset cerebellar ataxia. *Neurology*. 2008;71(4):301.
8. Patterson JR, Grabis M. Locked-in syndrome: a review of 139 cases. *Stroke*. 1986;17(4):758-764.
9. Lukowicz M, Matuszak K, Talar A. A misdiagnosed patient: 16 years of locked-in syndrome, the influence of rehabilitation. *Med Sci Monit*. 2010;16(2):CS18-CS23.
10. Corapcioglu F, Mutlu H, Kara B, et al. Response to rituximab and prednisolone for opsoclonus-myoclonus-ataxia syndrome in a child with ganglioblastoma. *Pediatr Hematol Oncol*. 2008;25(8):756-761.
11. Moretti R, Torre P, Antonello RM, Nasuelli D, Cazzato G. Opsoclonus-myoclonus syndrome: gabapentin as a new therapeutic proposal. *Eur J Neurol*. 2000;7(4):455-456.
12. Zee DS. Brainstem and cerebellar deficits in eye movement control. *Trans Ophthalmol Soc U K*. 1986;105(5):599-605.
13. Baets J, Pals P, Bergmans B, et al. Opsoclonus-myoclonus syndrome: a clinicopathological confrontation. *Acta Neurol Belg*. 2006;106(3):142-146.