

Neuropsychologic Assessment and Cognitive Rehabilitation in a Patient With Locked-In Syndrome and Left Neglect

Luigi Trojano, MD, Pasquale Moretta, PsyD, Anna Estraneo, MD, Lucio Santoro, MD

ABSTRACT. Trojano L, Moretta P, Estraneo A, Santoro L. Neuropsychologic assessment and cognitive rehabilitation in a patient with locked-in syndrome and left neglect. *Arch Phys Med Rehabil* 2010;91:498-502.

We describe a patient affected by severe incomplete locked-in syndrome (LIS) and left neglect caused by a combination of vascular lesions. Our patient's neglect prevented the use of augmentative communication devices based on a computerized eye-tracker system. For this reason, we adapted a visual scanning training for neglect rehabilitation. At the end of the rehabilitative training, the patient had regained full exploration of the monitor and could use the eye-tracker system for communicative purposes. This case report shows that specific rehabilitative approaches can be devised in severely disabled LIS patients with additional brain lesions and specific cognitive defects.

Key Word: Rehabilitation.

© 2010 by the American Congress of Rehabilitation Medicine

LOCKED-IN SYNDROME IS characterized by quadriplegia and anarthria with preserved consciousness, cognitive functions, and vertical eye movements.^{1,2} Patients affected by this classic form of LIS most often show an ischemic lesion in the ventral pons.³ Some patients may present other residual movements, such as horizontal eye movements and small head rotation; these cases are diagnosed as "incomplete" LIS and are caused by lesions encroaching on the ventral pons as well.³ LIS patients interact with the environment thanks to yes-no eye code responses, but brain-computer interface devices can exploit patients' eye movements for communicative purposes and for interaction with the environment.^{4,5} However, additional brain lesions may determine cognitive defects hindering the use of technological systems.⁶⁻⁸

In the present article, we describe a patient affected by severe incomplete LIS and left neglect caused by a combination of vascular lesions. Unilateral spatial neglect, frequently associated with right brain damage, consists in the failure to report, respond, or orient toward stimuli in the contralesional side of space.⁹ Typically, patients with neglect show prolonged observation times in the ipsilesional side during visual search, reading, or free viewing tasks; in such patients, contralesional saccades are fewer and slower to initiate with respect to ipsi-

sional saccades.^{10,11} Accordingly, left neglect prevented efficient employment of technological aids in our patient. Faced with this severe clinical picture, we developed a specific rehabilitation training aimed at allowing our patient to use an eye-tracker system for communicative purposes. At the end of the rehabilitation period, the patient had regained her ability to explore the monitor and interact with the computerized system to express her needs and feelings.

CASE REPORT

A 57-year-old right-handed woman developed multiple ischemic lesions secondary to endovascular embolization of a ruptured aneurysm of the right middle cerebral artery. After surgery, the patient presented prolonged unresponsiveness and was transferred to an intensive care unit where a score of 8 on the Glasgow Coma Scale¹² was recorded. The patient remained in a coma for about 20 days and eventually evolved to a vegetative state.¹³ One month after surgery, brain magnetic resonance imaging showed lesions in ventral pons and in deep periventricular white matter of the right temporoparietal region (fig 1).

Two months after onset, the patient was admitted in our department where a comprehensive neurorehabilitation program was started. On admission, a minimally conscious state was diagnosed¹⁴ because the patient showed inconsistent but reproducible sustained horizontal and vertical eye movements towards salient acoustic or visual stimuli (eg, visual pursuit of her family members) without any other movement. At that time, the patient was assigned a score of 2 on the Glasgow Outcome Scale-Extended¹⁵ and a score of 3 on the Levels of Cognitive Functioning Scale.¹⁶

In subsequent months, the patient's responsiveness gradually improved, and, at 6 months after onset, the patient gazed towards people speaking to her and had learned to use an eye-code communication system by keeping her eyes closed to mean affirmative responses and looking up for negative responses. At that time, she had recovered spontaneous respiration through a tracheostomy tube and was fed by means of enteral tube nutrition; she showed spared vertical and horizontal conjugated eye movements but showed lower cranial nerve palsy, severe dysphagia, and anarthria. No voluntary head or limb movement was possible, and there was presence of hyperreflexia and pyramidal signs; there was also sphincter incontinence. The patient could detect and localize somatosensory stimuli (touch) delivered to either side of her body. A simplified confrontation procedure did not reveal clinically evident visual field defects. The patient reacted to emotional stimuli with bursts of laughing or crying and could answer simple verbal and written questions via the eye-code system although her responses were slow and laborious (Glasgow Outcome Scale-Extended=3, Levels of Cognitive Functioning

From the Neuropsychology Lab, Department of Psychology, Second University of Naples (Trojano); Salvatore Maugeri Foundation, IRCCS, Scientific Institute of Telesse Terme (BN) (Trojano, Moretta, Estraneo); Department of Neurological Sciences, Federico II University (Santoro), Naples, Italy.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

Reprint requests to Luigi Trojano, MD, Dept of Psychology, Second University of Naples, Via Vivaldi 43, 81100 Caserta, Italy, e-mail: luigi.trojano@unina2.it.

0003-9993/10/9103-0037\$36.00/0
doi:10.1016/j.apmr.2009.10.033

List of Abbreviations

LIS	locked-in syndrome
-----	--------------------

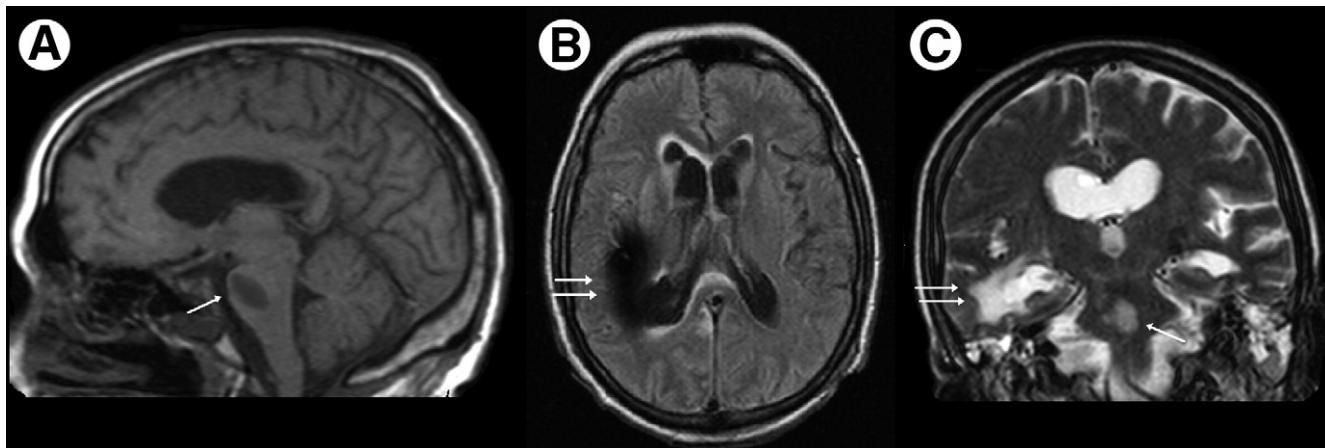


Fig 1. T1 sagittal (A), T1 axial (B), and T2 coronal (C) magnetic resonance scans showing T1-hypointense and T2-hyperintense ischemic lesions in the ventral pons (pointed to by a single arrow) and in deep periventricular white matter of the right temporoparietal region (pointed to by a double arrow).

Scale=6). Repeated formal functional assessment by means of the Coma Recovery Scale-Revised¹⁷ Italian version¹⁸ revealed that the patient attended to examiner's orders throughout the evaluation (arousal scale: 3/3), comprehended auditorily and visually presented sentences (communication scale: 2/2), consistently complied with auditorily perceived commands requiring eye responses (auditory function scale: 4/4), and could visually recognize objects (visual function scale: 5/5) but presented only flexion withdrawal limb movements to painful stimuli (motor function scale: 2/6) and oral reflex movements on lip stimulation (oromotor/verbal function scale: 1/3). These features clearly showed that our patient had recovered from a minimally conscious state although she presented a very severe motor impairment consistent with the diagnosis of incomplete locked-in syndrome (3). However, during formal assessment and in daily life, the patient tended to gaze preferentially toward her right side and showed apparent difficulties and delay in moving her eyes toward her left side, compatible with the presence of left neglect in association with the incomplete LIS. Such a combination of defects did not allow an extensive assessment of cognitive functions with the procedures specifically devised for LIS patients.^{6,7} Within the limits imposed by ocular fatigue on communicative eye movements, she appeared to be oriented in time and space and correctly replied to simple questions about word meaning and public events (semantic memory) and about past and recent events of her personal life (episodic memory); the attempts at assessing attention, reasoning, and executive functions with visuospatial material were hampered by the apparent visual exploration bias.

Because our patient had regained consistent and reproducible responsiveness, showed rather selective cognitive impairments, and could communicate only by means of eye code responses, we decided to use a computerized device based on eye-tracker technology to exploit her functional interactive skills. The patient gave her informed consent to the study; the study was approved by the local ethics committee.

BASELINE ASSESSMENT OF COMPUTER-INTERFACE USAGE

As a first step toward the use of augmentative communication devices, we assessed the patient's abilities to interact with a computerized eye-tracker system, and we used the same

apparatus to quantify her apparent rightward bias in eye movements.

Methods

Apparatus. Eye movements were recorded by a computerized infrared eye-tracker system^a with 50-Hz sampling frequency. The system is based on a 17-in monitor around which 4 infrared illuminators and sensors are located. The system is connected to a personal computer for task presentation and recording and analysis of eye-movement patterns. The patient sat at a 60-cm distance from the monitor, which covered a visual angle of 28°.

Procedure: interaction with the eye-tracker system. Three tasks were given to assess the patient's ability to use the electronic device. In the first (calibration) task, the patient was asked to pursue a colored circle slowly moving on the monitor and to fix it whenever it stopped and flashed (5 locations tested per trial, 5 trials for session). In the second task, the patient was required to look at 12 graphic buttons (arranged in a 3 × 4 grid) representing physical needs (eg, drinking, eating); 10 buttons were randomly assessed in each session, 5 per side. In the third task, the patient was asked to search for and fixate the letters on a simplified keyboard; in each session 10 letters were assessed on the left side, 10 in the central position and 10 on the right side. Instructions and stimuli were verbally presented. All 3 tasks were given in a fixed order in each session, and sessions were repeated 3 times a few days apart.

Eye-movement analysis. Two tasks were used for obtaining a representative measure of the patient's ability to move her gaze in spontaneous eye behavior. In the first task, the patient was asked to explore pictures of animals centered on 1 half (left or right) of the monitor while scrambled pictures (matched with stimuli for chromatic scale) appeared on the opposite half. Ten stimuli were presented on the left and 10 on the right half of the screen in a pseudorandom order; visual exploration time was set at 10 seconds per stimulus. In the second task, the patient was asked to look at her relatives' faces presented on 1 half of the screen while unfamiliar faces were shown on the opposite side. As described previously, 10 target stimuli were shown on the left and 10 on the right half of the screen in a pseudorandom order; each image was presented for 10 seconds. Among eye-movement parameters, we took into account

Table 1: Patient's Correct Responses on Computer Usage Tasks Before and After the Rehabilitative Program

	First Baseline	Second Baseline	End Treatment
Visual pursuit			
Left side	0/30	0/30	18/30*
Central position	2/15	1/15	15/15*
Right side	25/30	26/30	30/30
Looking at graphic buttons			
Left side	5/15	5/15	12/15*
Right side	14/15	13/15	15/15
Fixating letters			
Left side	3/30	8/30	26/30*
Central position	24/30	25/30	29/30
Right side	29/30	28/30	30/30

NOTE. No significant difference was observed in distribution of correct responses at the first and the second baseline for all measurements.

*Significantly different from respective baseline measurements (Fisher exact test $\leq .05$, 2-tailed).

the number of fixations and the total observation time that best express exploratory behavior in prolonged tasks.¹¹ Both tasks for eye movements were performed on 3 separate sessions a few days apart in different periods of the day.

To verify spontaneous evolution of the clinical picture over time and to get a further baseline assessment, the patient was evaluated again with the same procedure 1 month after the first evaluation.

Results and Comment

Computer-usage tasks showed that the patient could comply with task instructions and was potentially able to interact with the infrared eye-tracker system but was affected by a strong visual exploration bias toward the right side (table 1). A similar pattern was observed in the 2 tasks for the quantitative assessment of eye movements in which the number of fixations and the total observation time showed a significant asymmetry in the 2 hemifields (table 2).

One month after the first baseline assessment, virtually the same results were obtained, without significant differences of eye-movement parameters between the 2 evaluations (see tables 1 and 2). Such a stable asymmetry of visual exploration undermined the efficient use of augmentative communication software and induced us to devise a specific rehabilitative training.

REHABILITATIVE TRAINING

On the basis of well-established recommendations for applying visual-scanning strategies in rehabilitative treatment of visuospatial neglect,¹⁹ we implemented a traditional visual scanning training²⁰ for administration via the computerized eye-tracker system.

Procedure

Using the same apparatus as in the previous section, we devised progressive visual-scanning exercises. Stimuli consisted of colored circles (diameter: 5 cm; visual angle: 4.7°) displayed on a contrasting background. In the simplest exercises (level 1), stimuli appeared in a linear sequence from the right to the left and persisted on the screen for a long time (10 seconds); more complex exercises implied progressively shorter presentation times (level 2), a higher number of stimuli (level 3), and nonlinear presentation sequences (level 4). At the most complex level of difficulty (level 5), the number of stimuli, presentation time, and stimulus location varied from trial to trial and were not predictable. In each exercise, the patient was required to search and fixate to the targets, and, in case of failure, she was verbally encouraged to complete the task. Time spent over targets was recorded in each exercise, and when the patient performed at least 90% correct on 3 exercises of a given level, she was presented with exercises of the next level of complexity. The training started about 7 months after stroke, and lasted 4 weeks, with four 40-minute sessions per week.

Results and Comment

The patient gradually recovered her visual exploration skills during the training. In early sessions, she could fixate to targets only for 53% of the time at the first level of complexity. By the second week, she performed well on the first 2 levels and was 45% correct at the third level. At the end of the training, she could fixate to targets 85% of the time at the fifth level, thus showing a task-specific improvement.

END-TREATMENT ASSESSMENT

To verify possible generalization of the patient's task-specific improvements and in order to start using augmentative communication software, about 10 days after the end of the training (and about 9 months after stroke), we reassessed the patient on the same tasks as at the baseline.

Table 2: A Quantitative Assessment of Patient's Eye Movements Before and After the Rehabilitative Program

	First Baseline	Second Baseline	End Treatment
Animal task			
Fixation count: right side	17.3 \pm 3.26	17.9 \pm 3.31	18.5 \pm 3.54
Fixation count: left side	4.7 \pm 2.52*	4.8 \pm 2.43	14.6 \pm 3.61 [†]
Observation length: right side	457.13 \pm 205.47	455.51 \pm 234.33	466.23 \pm 290.79
Observation length: left side	413.35 \pm 172.69*	415.92 \pm 189.16*	467.34 \pm 293.83 [†]
Face task			
Fixation count: right side	18.6 \pm 4.12	18.3 \pm 3.96	18.1 \pm 3.44
Fixation count: left side	3.7 \pm 2.48*	4.2 \pm 2.67*	15.7 \pm 3.55 [†]
Observation length: right side	526.47 \pm 318.42	518.78 \pm 334.81	500.80 \pm 359.48
Observation length: left side	342.01 \pm 143.44*	352.32 \pm 154.03*	401.01 \pm 232.01 [†]

NOTE. Values are mean \pm SD unless otherwise indicated. No significant difference was observed between the first and the second baseline for all measurements (paired *t* tests).

*Significantly different from the right side (paired *t*₂₉ tests, *P* $\leq .001$ according to Bonferroni correction, 2-tailed).

[†]Significantly different from the 2 respective baseline measurements (paired *t*₂₉ tests, *P* $\leq .001$ according to Bonferroni correction, 2-tailed).

Results and Comment

The patient showed an obvious improvement of her ability to scan the visual array of needs and letters although she occasionally failed in fixating the leftmost stimuli (see table 1). The quantitative assessment of eye movements showed a significant change of number of fixations and observation time on the left side (see table 2).

DISCUSSION

LIS is a very disabling condition causing almost unbearable burden for patients and their families, but it may be complicated by additional cognitive or neurologic defects in relation to the extension, nature, and site of cerebral lesions.⁶⁻⁸ For instance, in a small sample of 10 patients with chronic LIS, a systematic neuropsychological assessment via a yes-no procedure revealed memory and attentional defects in 2 patients with thalamic lesions associated with the pontine damage and executive defects and language comprehension impairments in 1 patient with additional frontal and temporal damage.⁶ The patient described here showed an unfortunate combination of brain lesions determining a severe incomplete LIS associated with typical left neglect. This picture has never been reported previously, but it represents the natural consequence of the association of deep right temporoparietal damage²¹ with pontine lesions and could be recognized thanks to adequate assessment procedures.

In such cases special attention and further care and rehabilitative treatment are warranted. Actually, it has been underlined that in LIS patients' quality of life is entirely dependent on their arduous communication with the environment. Any clinically relevant cognitive deficit may reduce the efficiency of communication processes and the possibility of using the sophisticated patient-computer interfaces permitting LIS patients to communicate and even to control their environment.²²

To overcome additional limitations of the possibility to interact with the environment, determined by neglect in our patient, we devised a specific rehabilitative program tailored to the patient's clinical conditions. Manual or verbal responses were impossible, so we had to limit the training program to a visual scanning rehabilitative paradigm, specifically adapted for the eye-tracker system. Although we cannot estimate the role of spontaneous recovery in the evolution of the clinical picture, the positive outcome in our patient would be in line with controlled studies on neglect rehabilitation showing the efficacy of visual scanning training.¹⁹ Recent studies warn that visual scanning alone could have some limitations in neglect rehabilitation, particularly as far as possible generalization is concerned.²³ However, in the present case, we obtained evidence suggesting that the training program improved the patient's interaction with the eye-tracker system also on tasks using different kinds of stimuli. In this sense, the improvement of a visual scanning strategy was sufficiently generalized to allow more efficient use of augmentative communication devices. From these findings, we cannot exclude that the patient could still present defective explorative behavior on other kinds of tasks, but this possibility could not be quantitatively verified and was not particularly relevant for the patient's clinical conditions. Moreover, it is worth underlining that although the time schedule of our study (2 baseline assessments 1 month apart, end-treatment evaluation performed about 9 months after stroke) minimized the possible weight of spontaneous recovery, the present results did not allow strong inferences about the specific efficacy of our treatment because of the lack of control conditions. However, our case report shows that reha-

bilitative approaches can be devised in severely disabled LIS patients with additional brain lesions and cognitive defects.

In this perspective, it appears to be of paramount importance that there is an accurate evaluation of cognitive abilities in LIS patients, and, to this aim, specifically adapted testing procedures have been recently devised.^{6,24,25} In fact, specific cognitive defects have been observed even in LIS patients without evidence of hemispheric lesions.^{6,24} For instance, in a recent series of LIS patients with lesions centered on the brainstem,²⁴ it has been shown that several cases may show defects in relatively complex tasks involving complex sentence comprehension, mental calculation, and problem-solving abilities. Therefore, it is evident that tailored rehabilitation programs may be necessary to increase communication skills and to improve the quality of life in LIS patients with or without additional cortical lesions. We hope that the present case report will stimulate new efforts in detecting neuropsychological impairments and in designing cognitive rehabilitation programs to enable LIS patients to express their thoughts and feelings.²¹

References

1. Plum F, Posner JB. The diagnosis of stupor and coma. Philadelphia: FA Davis; 1966.
2. Smith E, Delargy M. Locked-in syndrome. Br Med J 2005;330:406-9.
3. Bauer G, Gesterbrand F, Rumpl E. Varieties of the locked-in syndrome. J Neurol 1979;221:77-91.
4. Casanova E, Lazzari RE, Lotta S, Mazzucchi A. Locked-in syndrome: improvement in the prognosis after an early intensive multidisciplinary rehabilitation. Arch Phys Med Rehabil 2003;84:862-7.
5. Söderholm S, Meinander M, Alaranta H. Augmentative and alternative communication methods in locked-in syndrome. J Rehabil Med 2001;33:235-9.
6. Schnakers C, Majerus S, Goldman S, et al. Cognitive function in the locked-in syndrome. J Neurol 2008;255:323-30.
7. Smart CM, Giacino JT, Cullen T, et al. A case of locked-in syndrome complicated by central deafness. Nat Clin Pract Neurol 2008;4:448-53.
8. Trojano L, Moretta P, Estraneo A. Communicating using the eyes without remembering it: cognitive rehabilitation in a severely brain-injured patient with amnesia, tetraplegia and anarthria. J Rehabil Med 2009;41:393-6.
9. Vallar G. Extrapeersonal visual unilateral spatial neglect and its neuroanatomy. Neuroimage 2001;14:S52-8.
10. Forti S, Humphreys GW, Watson DG. Eye movements in search in visual neglect. Vis Cog 2005;12:1143-60.
11. Behrmann M, Watt S, Black SE, Barton JJ. Impaired visual search in patients with unilateral neglect: an oculographic analysis. Neuropsychologia 1997;35:1445-58.
12. Teasdale G, Jennet B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81-4.
13. Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). N Engl J Med 1994;330:1499-508.
14. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58:349-53.
15. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the GOS and the GOS-E: guidelines for daily use. J Neurotrauma 1998;15:573-85.
16. Gouvier WD, Blanton PD, LaPorte KK, Nepomuceno C. Reliability and validity of the Disability Rating Scale and the Levels of Cognitive Functioning scale in monitoring recovery from severe head injury. Arch Phys Med Rehabil 1987;68:94-7.

17. Giacino JT, Kalmar K, Whyte J. The JFK Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004;85:2020-9.
18. Lombardi F, Gatta G, Sacco S, Muratori A, Carolei A. The Italian version of the Coma Recovery Scale-Revised (CRS-R). *Fun Neurol* 2007;22:47-61.
19. Cicerone KD, Dahlberg C, Malec JF, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch Phys Med Rehabil* 2005;86:1681-92.
20. Antonucci G, Guariglia C, Judica A, et al. Effectiveness of neglect rehabilitation in a randomized group study. *J Clin Exp Neuropsychol* 1995;17:383-9.
21. Dorigatti F, Thiebaut de Schotten M, Tomaiauolo F, Bartolomeo P. White matter (dis)connections and gray matter (dys)functions in visual neglect: gaining insights into the brain networks of spatial awareness. *Cortex* 2008;44:983-95.
22. Laureys S, Pellas F, Van Eeckhout P, et al. The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? *Prog Brain Res* 2005;150:495-511.
23. Keller I, Gudrun LR, Losch J, Kerkhoff G. Combination of pursuit eye movement training with prism adaptation and arm movements in neglect therapy: a pilot study. *Neurorehabil Neural Repair* 2009;23:58-66.
24. Rousseaux M, Castelnau E, Rigaux P, Kozlowski O, Danzé F. Evidence of persisting cognitive impairments in a case series of patients with locked-in syndrome. *J Neurol Neurosurg Psychiatr* 2009;80:166-70.
25. Vallar G, Cappa SF. Articulation and verbal short-term memory. Evidence from anarthria. *Cog Neuropsychol* 1987;4:55-78.

Supplier

- a. Tobii Technology, Box 743, S-182 17, Danderyd, Sweden.