Clinical review

Locked-in syndrome

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The locked-in syndrome is caused by an insult to the ventral pons, most commonly an infarct, haemorrhage, or trauma. The characteristics of the syndrome are quadriplegia and anarthria with preservation of consciousness. Patients retain vertical eye movement, facilitating non-verbal communication. Ten year survival rates as high as 80% have been reported. Even limited physical recovery can improve quality of life and enable patients to return to live with their families. Early referral to a specialist rehabilitation service for specialist care and technology is therefore important.

Summary points

- Life expectancy has improved for patients with locked-in syndrome
- Early specialist rehabilitation aids patients to regain some function
- Establishing an effective communication system should be an early target
- Engaging the family in rehabilitation may enable eventual return home
- Despite profound disability, patients don't necessarily want to die

Sources and selection criteria

We gathered information for this article through searches in Medline and Taylor and Francis Health Sciences, identifying relevant case series reviews on the locked-in syndrome and other brain stem strokes. Our own experience is also incorporated.

Clinical features

Locked–in syndrome was first defined in 1966 as quadriplegia, lower cranial nerve paralysis, and mutism with preservation of consciousness, vertical gaze, and upper eyelid movement.[1] It was redefined in 1986 as quadriplegia and anarthria with preservation of consciousness.[2] This redefinition served to clarify that mutism could imply unwillingness to speak.[3]

Although patients are conscious, attention, executive function, intellectual ability, perception, and visual and verbal memory can be affected.[4] Leon-Carrion and colleagues reviewed 44 patients with the locked-in syndrome, of whom eight reported memory problems and six attentional deficits.[5] Memory difficulties were more likely when the aetiology was traumatic.[5] However, in a report of two patients with chronic locked-in syndrome, neuropsychological assessment showed preserved cognitive abilities.[6]

A review by Zeman of consciousness indicated that cerebral metabolism, as monitored by positron emission tomography, is only mildly reduced in locked-in syndrome but severely reduced in the vegetative state.[7] The electroencephalogram typically shows slow wave activity in the vegetative state but normal activity in locked-in syndrome.

Anarthria is due to bilateral facio-glosso-pharyngo-laryngeal paralysis,[8] which also causes dysphagia and limits the use of facial expression in communication. Although medial and lateral gaze palsies are typical, patients usually retain upper eyelid control and vertical eye movement because of sparing of the mid-brain tectum, which allows communication. In our experience, hearing is well preserved, but visual difficulties can arise from blurring, diplopia, and impaired accommodation. Other complications include vertigo, insomnia,[9] and emotional lability.[5] In one group of patients who recovered from locked-in syndrome, six out of 44 reported visual deficits and 39 stated that they cried or laughed more easily since the onset.[5] Pulmonary complications are the leading cause of death and, as in high spinal cord injury, are compounded by reduced vital capacity. Aspiration of saliva, due to dysphagia and impaired cough reflex, leads to further complications, including atelectasis and pneumonia; immobility predisposes to pulmonary embolus.[10]

Classification

Locked-in syndrome has been classified into three categories[11]:

Classic—Quadriplegia and anarthria with preserved consciousness and vertical eye movement

Incomplete—The same as classic but with remnants of voluntary movement other than vertical eye movement

Total—Total immobility and inability to communicate, with full consciousness.

This classification has been referred to in previous case series reports,[3 8 9] but no management details are given which differentiate the categories. Each of the

three categories has been subdivided into transient and chronic forms.[11] Patients with transient locked-in syndrome improve neurologically; an episode of locked-in syndrome that lasted only a few minutes, with good recovery, has been reported.[12]

Diagnosis and early management

Typically, locked-in syndrome is caused by an insult to the ventral pons, although extensive bilateral destruction of corticobulbar and corticospinal tracts in the cerebral peduncles may also be responsible (table 1).[2 3 5 9 13 14] The diagnosis can be missed if voluntary vertical eye movement is not assessed in patients who seem unresponsive. When magnetic resonance imaging shows a ventral pontine insult in an otherwise unresponsive patient, the assessor should re-examine vertical eye movement. Locked-in syndrome can be difficult to diagnose because some patients emerge from coma into a locked-in state after a variable delay. The diagnosis of locked-in syndrome is often triggered by a member of the care staff or family reporting awareness. Leon-Carrion and colleagues found that in just over half of cases the first person to realise that the patient was aware and able to communicate was a family member.[5] In that study the mean time to diagnosis was 78.8 days.[5] This is a very rare condition, for which we could not find an incidence.

The acute management of patients with locked-in syndrome is similar to that for patients with other acute brain stem insults. The initial emphasis is on maintaining an airway and adequate oxygenation. Managing reversible medical causes and reducing risk factors are essential while preventing the complications of immobility, dysphagia, and incontinence. Chest physiotherapy, including deep breathing exercises, frequent positional changes, postural drainage, and suctioning, may limit pulmonary complications. Corneal ulceration, due to impaired eye closure, can be treated by lateral tarsorrhaphy or botulinum therapy. Avoiding full eye closure is important because it will prevent communication. Pathological crying can respond to selective serotonin reuptake inhibitors.

Recovery and prognosis

Early literature, primarily relying on autopsy findings, reported that long term survival was rare without neurological recovery. In 1986, mortality was estimated at 60%, being greatest in the first four months and higher in patients with vascular insult than non-vascular causes.[13] Survivors tended to be younger at age of onset. Earlier rehabilitation and more effective nursing care have recently been reported to reduce mortality from acute locked-in syndrome.[9] Casanova et al reported that patients with locked-in syndrome who began rehabilitation within one month of the acute event had a mortality of only 14% at five years.[9] Although most survivors remain either in a chronic locked-in state or severely impaired, early signs of recovery can be exploited through multidisciplinary rehabilitation.[2 3 8 9 13 14] In our rehabilitation programme, we monitor for recovery of thumb, finger, head, and neck movement; evidence of independent swallow; and improvement in respiratory function. Any movement that may enable the patient to use a buzzer, an environmental control, or a communication device is targeted.[15]

Table 1 Causes and mechanisms of locked-in syndrome

Cause	Mechanism
Ischaemic	Basilar artery occlusion, hypotensive or hypoxic events
Haemorrhage	Haemorrhage originating within or infiltrating into the pons
Traumatic	Direct brain stem contusion or vertebrobasilar axis dissection
Tumour	Primary or secondary infiltration of the ventral pons
Metabolic	Central pontine myelinolysis
Demyelination	Multiple sclerosis affecting the ventral pons
Infectious	Abscess infiltrating the ventral pons, brain stem encephalitis

Patients initially tire quickly when using vertical eye movement to communicate. Furthermore, their attention span may be severely limited in the first few weeks or months. An agreed system of interpretation is necessary, where one upward movement signifies yes and two rapid upward movements, no. Effective questioning skills must be developed, avoiding open ended questions and confirming answers by repeating questions when necessary. Aggressive treatment of infections, respiratory difficulties, pain, or localised problems such as corneal abrasions can enhance physical stamina and communication. Because patients with classic locked-in syndrome are unable to call for attention or initiate conversation, they should frequently be given the opportunity to communicate and, indeed, end dialogue.

The only aspect of locked-in syndrome recovery for which we found a classification is motor recovery (box).[13] No specific classification systems exist for vocal, dysphagia, cognitive, emotional, or behavioural recoveries. A retrospective review of 53 patients with other brain stem strokes used the modified Barthel index to measure functional outcomes such as limb weakness, ataxia, dysarthria, dysphasia, and urinary continence, but emotional and behavioural recoveries remain unclear.[16]

Table 2 summarises the findings from three studies examining life expectancy and functional recovery in patients with locked-in syndrome.[8 9 14] This overview suggests that with return of greater respiratory effort, some swallowing ability, and improved continence, the need for tracheostomies, gastrostomies, and urinary catheters reduces with time.[8 9] All patients with locked-in syndrome should be rehabilitated in a national or regional specialist centre that has specific multidisciplinary rehabilitation experience with the condition. Although cognitive ability should not be overestimated, survivors' views regarding the focus of acute treatment, rehabilitation goals, and life choices should be formally sought.

Classification of recovery of motor function[13]

No recovery—No return of motor function, total dependence for all activities of daily living
Minimal recovery—Minimal motor return, total dependence for all activities of daily living
Moderate recovery—Moderate motor return, independence in some but not all activities of daily living
Full recovery—Independence in all activities of daily living but some minimal neurological deficit
No neurological deficit—No reported residual deficits

Table 2 Findings from three case series of patients with locked-in syndrome. Values are numbers (percentages) unless stated otherwise

Variable	Doble 2003[14] (USA)	Casanova 2003[9] (Italy)	Richard 1995[8] (France)
Mean age of onset (years)	33.6	44.7	45.3
Age range at onset (years)	1-70	16-71	17-73
No of males/females	19/10	9/5	9/2
Aetiology:			
Vascular	15 (52)	11(79)	10 (91)
Traumatic	9 (31)	3 (21)	1 (9)
Other	5 (17)	0	0
Survival rates (%):			
5 years	83	86	NA
10 years	83	NA	NA
20 years	40	NA	NA
Motor recovery	16 (55)	11 (79)	10 (91)
Respiratory improvement	NA	8 (58)	10 (91)
Emergence of swallow	20(69)	6 (42)	8 (73)
Basic verbal communication	9 (31)	4 (28)	4 (36)
Bowel continence	4 (14)	5 (35)	NA
Bladder continence	7 (24)	5 (35)	10 (100)
Returned to live with family	19 (65)	8 (57)	8 (73)

Development of communication devices

Patient-computer interfaces such as infrared eye movement sensors and computer voice prosthetics are being further developed by rehabilitation engineers and speech language therapists.[14] Computers have had a liberating effect on the lives of people with locked-in syndrome, enabling them to initiate dialogue, prepare questions or other messages, and use the internet. When augmentative communication devices are added to a computer, patients who remain unable to talk may find a way to communicate widely. Sophisticated technology needs to be backed up by the simple, cheap, and portable alphabet board. Patients who recover distal movement can point to the letters; otherwise, a family member or carer can facilitate use of the board (figure).[17] A well used communication book containing daily activities, news events, visits, and programme changes can help keep everyone up to date.

Quality of life for patients and carers

Many patients choose to return to live at home, which presumably enables greater social interaction with family and friends.[8 9 14] Return to home life may positively influence the patient's desire to live.[14] However, it places a long term physical and psychological burden on the family. Limited funding means that community care is often scarce and the carers are poorly supported.

We found only two references to patients who returned to work. The first was a lawyer who used morse code blinks to provide legal opinions and the second was someone who taught maths and spelling using a mouth stick to trigger an electronic voice device.[14]

A	B	C	D	End of word	
E	F	G	H	End of sentence	
I	J	K	L	M	N
O	P	Q	R	S	T
U	V	W	X	Y	Z

AEIOU alphabet board. The assistant calls out the colours and the patient signals the required colour by an upward eye movement. The assistant then sequentially calls out the letters on that line. The chosen letters are written down to formulate a sentence, question, or statement.

Patient information

Bauby J-D. *The diving bell and the butterfly: a memoir of life in death.* New York: Vintage, 1996.
Association for the Locked-in Syndrome (ALIS) (www.club-internet.fr/alis)
National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov/disorders/lockedinsyndrome/lockedinsyndrome.htm)

In the only review of quality of life, the authors found that a series of seven patients with locked-in syndrome had a worse quality of life on the Spitzer quality of life index than cancer patients but better than terminally ill patients; of the five who completed the general health questionnaire, three were depressed, but they all stated that they would want antibiotics if they developed pneumonia.[18] In the longest surviving group of patients reviewed (after 11 years) 54% had never considered euthanasia, 46% had previously considered it, and none had a "not for resuscitation" order.[14] The finding that locked-in syndrome survivors who remain severely disabled rarely want to die[14] counters a popular misconception that such patients would have been better off dead.

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1 Plum F, Posner JB. *The diagnosis of stupor and coma.* Philadelphia, PA: FA Davis, 1966.
2 Haig AJ, Katz RT, Sahgal V. Mortality and complications of the locked-in syndrome. *Arch Phys Med Rehabil* 1987;68:24-7.
3 Katz RT, Haig AJ, Clark BB, Di Paolo RJ. Long-term survival, prognosis and life-care planning for 29 patients with chronic locked-in syndrome. *Arch Phys Med Rehabil* 1992;73:403-8.
4 Garrard P, Bradshaw D, Jager HR, Thompson AJ, Losseff N, Playford D. Cognitive dysfunction after isolated brain stem insult. An underdiagnosed cause of long term morbidity. *J Neurol Neurosurg Psychiatry* 2002;73:191-4.
5 Leon-Carrion J, van Eeckhout P, Dominguez-Morales Mdel R, Perez Santamaria FJ. The locked-in syndrome: a syndrome looking for a therapy. *Brain Inj* 2002;16:571-82.

6 Allain P, Joseph PA, Isambert JL, Le Gall D, Emile J. Cognitive functions in chronic locked-in syndrome: a report of two cases. *Cortex* 1998;34:629-34.
7 Zeman A. What is consciousness and what does it mean for the persistent vegetative state? *Adv Clin Neurosci Rehabil* 2003;3:12-4.
8 Richard I, Pereon Y, Guiheneu P, Nogues B, Perrouin-Verbe B, Mathe JF. Persistence of distal motor control in the locked-in syndrome. Review of 11 patients. *Paraplegia* 1995;33:640-6.
9 Casanova E, Lazzari RE, Latta S, Mazzucchi A. Locked-in syndrome: improvement in the prognosis after an early intensive multi-disciplinary rehabilitation. *Arch Phys Med Rehabil* 2003;84:862-7.
10 Fishburn MJ, Marino RJ, Ditunno JF. Atelectasis and pneumonia in acute spinal cord injury. *Arch Phys Med Rehabil* 1990;71:197-200.
11 Bauer G, Gerstenbrand F, Rumpl E. Varieties of locked-in syndrome. *J Neurol* 1979;221:77-91.
12 Khurana RK, Genut AA, Yannakis GD. Locked-in syndrome with recovery. *Ann Neurol* 1980;8:439-41.
13 Patterson JR, Grabois M. Locked-in syndrome:a review of 139 cases. *Stroke* 1986;17:758-64.
14 Doble JE, Haig AJ, Anderson C, Katz R. Impairment, activity, participation, life satisfaction and survival in persons with locked-in syndrome for over a decade. *J Head Trauma Rehabil* 2003;5:435-44.
15 Söderholm S, Meinander M, Alaranta H. Augmentative and alternative communication methods in locked-in syndrome. *J Rehabil Med* 2001;33:235-9.
16 Chua KSG, Kong KH. Functional outcome in brain stem stroke patients after rehabilitation. *Arch Phys Med Rehabil* 1996;77:194-7.
17 Wu Y, Voda JA. User-friendly communication board for non-verbal, severely physically, disabled individuals. *Arch Phys Med Rehabil* 1985;66:82-8.
18 Anderson C, Dillon C, Burns R Life-sustaining treatment and locked-in syndrome. *Lancet* 1993;342:867–8.

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Evidence based case report

Use of antibiotics in suspected haemolytic-uraemic syndrome

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An 11 year old girl was admitted to our specialist paediatric intensive care unit under the joint care of paediatric intensivists and nephrologists. She had presented to her local hospital with a four day history of vomiting, diarrhoea, and becoming progressively more unwell. Initial blood tests showed acute renal failure and thrombocytopenia. We tentatively diagnosed haemolytic uraemic syndrome, although sepsis with renal dysfunction was part of the differential. These uncertainties arose because her blood film was not typical of haemolytic uraemic syndrome, she had a clotting abnormality, and we had no microbiological confirmation. Treatment with broad spectrum antibiotics was proposed. Some doubt remained about this treatment, however, because of a well publicised study suggesting that giving antibiotics to patients with *Escherichia coli* 0157:H7 enteritis could worsen haemolytic uraemic syndrome. We used a five step evidence based approach to address this problem.

Formulate the question

The first step in our approach was to formulate an answerable clinical question: In children with suspected haemolytic uraemic syndrome, particularly associated with *E coli* 0157:H7 infection, does treatment with antibiotics lead to increased morbidity, particularly progressive haemolytic uraemic syndrome or sepsis, compared with withholding antibiotics?

Acquire some information

Ideally this question would be answered by large randomised controlled trials. If trials were absent or inadequate, cohort studies or well conducted case-control reports would be helpful. As systematic reviews are increasingly used in all areas of research (not just randomised controlled trials) we looked first for such reports. Not expecting to find randomised controlled trials, we looked for studies using the PubMed clinical queries systematic review filter rather than the Cochrane Library. The search terms "hemolytic uremic syndrome AND antibiotics" returned three citations. Only one of these was a relevant systematic review of trials and observational studies.[1] As this was published in 2002, we searched for more recent relevant individual studies and found none.

Appraise the evidence

We used a combination of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal[2] and the Grading of Recommendations Assessment Development and Evaluation (GRADE) Working Group approach[3] to appraise and summarise the information. The MOOSE proposal sets out criteria for the effective reporting of meta-analysis in observational studies. The GRADE group is an international collaboration of clinicians and epidemiologists involved in the development of a unified system to support clinical practice recommendations.

The authors of the systematic review searched electronic databases, reference lists, and an ongoing trials database and consulted relevant experts to discover any rigorous study looking at the association between *E coli* 0157:H7 enteritis, antibiotic use, and development of haemolytic uraemic syndrome.[1] Studies were independently abstracted, and the reviewers used predetermined appraisal criteria. The results were pooled by using a fixed effects model, a funnel plot showed no asymmetry, and heterogeneity was appropriately explored.

The results of the review are summarised in the GRADE evidence profile (tables 1 and 2). The studies, which included two small randomised

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Table 1 Quality assessment of trials in systematic review for outcome development of haemolytic uraemic syndrome[1]

No of studies comparing antibiotics with no antibiotics	Design	Limitations	Consistency	Directness	Other modifiers
10	2 RCT, 3 cohort, 5 case-control	No serious limitations	Inconsistent*	Direct	Possible publication bias*

*Results of two studies were greatly different from the other eight, showing increased likelihood of haemolytic uraemic syndrome with antibiotics. When these were removed, there was no heterogeneity. This could be due to reverse publication bias.