"Locked-in" Syndrome: Introduction, Overview and Literature Review

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Abstract:

The following is a review article discussing a syndrome so rare that we infrequently study, discuss or acknowledge its existence. With that being said, we also challenge the previous statement by proposing en masse misdiagnosis of the condition in healthcare facilities.

Aim:

With the publication of this article, we hope to bring "Locked in" Syndrome the attention it deserves, as well as provide aid in properly diagnosing LIS. The author is keen on bringing an end to our intellectual poverty.

Introduction

"Locked in" syndrome, also known as "the locked-in state", "De-efferented state" "pseudocoma" [1] and "cerebromedullospinal disconnexion" [10] is a condition in which the patient is, in the most comprehensible of terms, *"locked-in"* their own bodies. Patients suffering from LIS is frightening for patients and their loved ones, the outcomes (discussed later) do not make it any easier. Patients are in a coma-like state with the exception of certain eye movements (discussed in the clinical presentations section of this article) which could increase the difficulty of differentiating between LIS and a coma. The awareness patients have to their surroundings may also require the consultation of a psychiatrist for both the patient and their loved ones. There are different types of LIS which we will be discussing in a separate section of this article. It is, however, important to keep it in mind.

History of LIS

As far as we can tell, the first liturgical appearance of LIS was back in the 1800s in Alexandre Dumas'[2] (1802-1870) well-known novel 'The Count of Monte Cristo'. In the novel, a character - M. Noirtier de Villefort – experiences an episode of what seems to be apoplexy that completely paralyzes him, with the exception of his eye movements which he uses as a form of communication. In medical literature, however, LIS took approximately a century to appear in the form we know of today. That can be attributed to Plum and Posner [3] who, in 1966, introduced to medical literature the term "Locked-in" Syndrome to define "a neurological condition associated with infarction of the ventral pons" [1]. The effect this had on our understanding of LIS was extraordinary. Although LIS was named in 1966; case reports dating back to 1875 [10] seem to have touched in some way, shape or form on the topic. Following the nomenclature of 1966, some reports – such as that of Chase et al. that was published in 1968 started to appear on the horizon [10]. One of the reports that played a major role in bringing attention to LIS was that by Norrrdgren et. al., in 1971 wherein 7 such cases were discussed [10]. The 2007 edition of

their book 'Diagnosis of Stupor and Coma' [4], which is now edited by Sid Gilman and William J. Herdman also discussed LIS (referred to therein as Locked in State) and defined it as "(a) condition with severe motor disability". In their, you will find a discussion of surveys and numerous papers published with a table that beautifully illustrates the point they intended to bring forth. Back in late 2007, LIS received an exponential rise in popularity amongst the masses with the release of the French drama 'Diving Bell and the Butterfly' (released in the USA) [5]. In the drama, the star character Jean-Dominique Bauby, who is the editor-in-chief of Elle fashion magazine, suffer a stroke that renders him paralyzed with the exception of minimal eye movement (blinking) (i.e. LIS). The movie goes on to heartbreakingly, yet beautifully, illustrate the suffering LIS patients experience. Back in 2014, Allison O'Reilly published 'Out of the Darkness: An inspirational Story of Survival in the Face of Stroke and Locked-In Syndrome' [7]. In the book, O'Reilly's story as a 49-year old with a successful career in a fortune 100 company who was suddenly paralyzed is depicted in an outstanding manner.
In 2018; Veronika Kubickova, Anita Rose and Barbra Wilson's book 'Locked-in Syndrome After Brain Damage: Living Within My Head' [8] was published. The book discussed the story of Paul Allen who suffers from LIS following a stroke.
During the writing of this article, the Daily Mail [6] published the story of 29-year old Anstey Campbell who suffered a month-long episode of LIS secondary to Guillian-Barre. As per the report, her only symptom was a feeling of tingling and pins in her toes, which she attributed to her new running shoes. She was, however, concerned when the sensation started to spread to her fingertips and payed her local GP a visit who didn't think much of it (they thought it was anxiety) and told her to visit him the next day if she is still concerned. Unfortunately, Anstey was not presented with that opportunity as her condition worsened overnight and she was admitted to hospital where she was later diagnosed with GBS.
In 2008, a paper published by Schnakers et. al. [13], demonstrated LIS patients' maintenance of cognitive function. That discover has aide in increasing our understanding of LIS.
Many more publications have been made. Unfortunately, LIS is, as of this writing, to many hitherto unheard of.

Types/varieties of LIS

As medical professional, we appreciate orderliness as it helps us act in a quick, efficient manner (for example: knowing where everything is in an Operation room or where medications are in an ER). This proclivity (which some might attribute to the type of personality needed for one to become a doctor (orderly and hyper-industrious)) towards orderliness has resulted in a longing for categorization so that not only can we properly diagnose cases, but so that we can also know how to create guidelines for other physicians to follow.

This has resulted in the categorization of LIS into:

1) Classical
2) Incomplete, and
3) Total

Classical LIS refers to conditions like those explained in Plum and Posner's aforementioned 1966 publication [3] in which patients exhibit "quadriplegia, lower cranial nerve paralysis, and mutism with preservation of only vertical gaze and upper eyelid movement" [1].

"The Incomplete category is similar to the Classical variety except that the patients have remnants of voluntary motion besides upper eyelid and vertical eye movement." [1]

"The Total variety is composed of a group of patients who are totally immobile, and are unable to communicate." [1]
"These patients are aware of both internal and external stimuli but are able to carry on only an internal monologue." [1]

In 1979, Bauer et. al. [9] proposed an alternative classification, that is:

1) Transient, and
2) Chronic

Another classification of LIS s dependent on the causation, that is:

1) Vascular, and
2) Non-vascular

LIS in ALS patients

By now, you have become quite familiar with LIS, but what is ALS and what are the differences? In the upcoming paragraphs, we will be answering that exact question. LIS does not occur in ALS patients only, but it is worth noting the points made by Bruno et. al. [11] in their 2007 paper including, but not limited to, the ethical aspect.

To be able to start, we first need to define both terms and since you have been familiarized with LIS, we will be discussing Amyotrophic Lateral Sclerosis (ALS). ALS is a ruinous neurodegenerative disorder that gradually paralyses patients until it is eventually able to stop them from breathing [11]. A 2008 paper by Lakerveld and colleagues [12] demonstrated quite convincingly the likely possibility of cognitive function preservation in ALS patients (can also be applied generally to those with motor neurological impairments). LIS is an expected complication of ALS.

In their paper, Bruno [11] and colleagues discuss the ethical aspect of ALS and LIS, with special consideration to their rights as far as euthanasia and DNR are concerned. This is what they wrote in their paper:

"By validating adapted neuropsychological testing and by demonstrating preserved cognition in patients with devastating motor neurological lesions, the study of Lakerveld and colleagues1 has important medical–ethical implications. It underscores the right of these patients to autonomy and demonstrates their ability to exercise it, including taking end of life decisions. For patients with no residual motor responses, additional investigations will have to be performed before this ultimate liberty can also be extended to them. This demonstration in ALS of patients' right to autonomy and capability of exercising it will reduce the ethical dilemmas of caregivers but not their responsibilities. Huge challenges remain. Firstly, it will be necessary for caregivers to provide all of the information that is necessary to validly exercise autonomy and then to ask all relevant questions. Moreover, they will have to phrase questions in such terms that they can unambiguously be answered by yes or no. The latter is tantamount to making the complex realm of existence, ideas, feelings and volitions binary. Secondly, many additional conditions need to be fulfilled for autonomy to be full autonomy. Indeed, to quote Harsanyi, ''… we have to (…) distinguish between a person's manifest preferences and his true preferences. […] A person's true

preferences are the preferences he would have if he had all the relevant factual information, always reasoned with the greatest possible care, and were in a state of mind most conducive to rational choice''.6 The beauty of medical and communication–
technological progress for patients with severe neurological conditions is that it makes them more and more like the rest of us. As a corollary, we caregivers not only owe them the same respect in terms of their autonomy as all other patients, but we also have to rise to so far seldom attained levels of clarity in matters of life and death."[11]

I wanted to paraphrase the findings, but they have articulated their ideas forthrightly and in such an eloquent manner that it left me no choice but to copy it as is.

Outcome of LIS

Although major efforts are taking place by those who are aware of LIS and are striving to change the current situation – the outcomes of LIS continue to be tragic, usually ending with some form of respiratory complication and death. We believe an increase in research efforts would largely aid in our progress towards changing this. As far as we can tell, statistics have barely changed since the 1987 publication by Haig et. al., [14] in which they stated that 75% of reported causes of death were pulmonary in nature.

Reported cases from around the world

In this section of the article, we will be pasting case reports from different journals around the world with the hope that it increases the readers' awareness of LIS. Keep in mind that some of the symptoms mentioned below might not have appeared earlier due to how rarely they manifest themselves.

CASE DESCRIPTION

1) "A 56-year-old male with history of alcohol abuse was admitted to our trauma service following a motor vehicle collision, where he was a passenger. The patient was found unresponsive with a Glasgow Coma Score of 3 (E1, V1, M1). Initial brain imaging demonstrated small subdural hematoma along the falx cerebri as well as the frontal convexities. A cervical spine magnetic resonance imaging (MRI) demonstrated severe post-traumatic changes at C5 - C6 level without evidence of cord compression. The patient regained consciousness 36 hours after admission. His neurological examination one week later was remarkable for an awake patient able to blink on command. Pupils were equal and reactive and extraocular movements had restricted bilateral abduction. Remaining bilateral vertical eye movements were intact. He had bilateral facial, lingual, and palatal weakness that impaired articulation, swallowing, and respiratory ability. He had flaccid quadriplegia with hyper-reflexia and bilateral Hoffman signs were present,

and he required full ventilator support through tracheostomy. His neurological examination was consistent with "Locked-in Syndrome",1 suggestive of a lesion at the level of the pons. MRI of the brain demonstrated symmetric areas of subtle restricted diffusion at pons and medulla involving corticospinal and corticobulbar fibers, suggestive of brainstem traumatic axonal injury." [15]

2) [10] "A 35-year-old normotensive housewife was well until February 1973, when she developed pain in the neck followed immediately by vertigo, diplopia, left hemiparesis, and slurred speech. Twenty four hours later she was unable to move any limb or indeed any muscle except for those of the eye and eyelid. Next morning arch aortography showed a tapering occlusion of the right vertebral artery 1 cm distal to its origin and hypoplasia of the left vertebral artery. The presumptive diagnosis was a locked-in state due to pontine infarction.

Her eyes moved up or down on command but chiefly down. The left eye could be completely shut but the right only partially Eo and there were no lower facial movements at all. The pupils were slightly constricted, more so on the right, but their light and accommodation reactions were preserved. The jaw was tightly clenched and could not be moved voluntarily and there was total paralysis of the tongue, palate, pharynx, and neck. Likewise there was no voluntary limb movement present but painful stimulation brought about a decerebrate posture. Hearing was grossly intact. There was flaccidity of the right arm and leg whereas the left limbs were mildly spastic. All the tendon jerks were present (brisker on the left) and both plantar responses were extensor. Sensation to touch was impaired on the left but intact on the right.

Both the ciliospinal and "doll's-head" reflexes were absent. Icecold irrigation of the ears, however, induced tonic lateral deviation of the eyes towards the cooled side. Thereafter her condition remained unchanged until six weeks later, when she developed a respiratory infection from which she died.

Apart from the bronchopneumonia and an old caseous tuberculous lymph node in the chest necropsy showed nothing abnormal outside the central nervous system. The basilar artery was normal but the left vertebral artery was less than 1 rmm in diameter. The right vertebral was completely occluded by thrombus extending almost to the vertebrobasilar junction. There was softening in the pons and right cerebellar hemisphere whereas the cerebral hemispheres were intact.

Microscopical examination of the vertebral artery showed that it was occluded by organized thrombus. The internal elastic lamina was virtually intact but much of the media was destroyed and had been replaced by granulation tissue. There was no sign of arteritis in any vessel.

Sections through the brain stem showed a large area of infarction affecting the ventral pons with slight dorsal extension. The cerebellar lesion consisted of a zone of cystic malacia involving the superior aspect of the right hemisphere. Microscopical examination of the cerebral cortex showed no abnormality." [10]

Recommendations

As medical personnel we possess, for the lack of a better word, a superpower. That superpower is the trust of the public. Unfortunately, we sometimes fail to meet our patients' expectations.

One of the reasons we fail to do so is because of our ignorance to the problems that they may be facing. We hereby recommend doctors not only educate one another of what LIS is, but to recommend neurology teams to always keep it in mind as a differential diagnosis whenever they may be conducting their physical exams. It is important that we not only meet our patients' expectations, but that we exceed them in a manner hitherto unimaginable.

Conclusion

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Abbreviations:
LIS = Locked-in Syndrome
GBS = Guillian–Barre Syndrome
ALS = Amyotrophic lateral sclerosis

Key words:
LIS; ALS; Stroke; Neuropsychiatry; Cognition; Infrequently researched conditions; TBIs, Brain injuries;