Rehabilitação de Síndrome de Lance-Adams: Caso Clínico

Rehabilitation of Lance-Adams Syndrome: A Case Report

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Resumo

Síndrome de Lance-Adams, ou mioclonias crónicas pós-hipóxia, é uma complicação rara de reanimação cardiopulmonar bem-sucedida e está geralmente associado a ataxia cerebelosa. Os autores relatam um caso de um doente de 41 anos que desenvolveu quadro clínico de disartria, tetraplegia, mioclonias severas, disdiadococinésia e ataxia cerebelosa após paragem respiratória no contexto de tratamentos de quimioterapia. Estes sintomas resultaram em consequências funcionais graves com incapacidade para o ortostatismo e para as actividades de vida diária. Foi assumido o diagnóstico de encefalopatia hipóxica com síndrome Lance-Adams. A implementação de tratamento farmacológico em conjunto com um programa interdisciplinar intensivo de reabilitação resultou em melhoria sintomática e funcional marcada permitindo a realização autónoma de actividades de vida diária e deambulação supervisionada após 7 meses. O presente artigo tem como objectivo reforçar a importância do diagnóstico correcto e tratamento adequado da síndrome de Lance-Adams, conduzindo à melhoria dos resultados funcionais destes doentes.

Palavras-chave: Mioclonia/reabilitação

Abstract

Lance-Adams syndrome, or chronic posthypoxic myoclonus, is a rare complication of successful cardiopulmonary resuscitation often associated with cerebellar ataxia. The authors report a 41-year-old patient who presented with clinical features of dysarthria, tetraplegia, severe myoclonus, dysdiadokinetia and cerebellar ataxia after respiratory arrest in the context of chemotherapy treatment. These symptoms resulted in marked functional consequences with inability to stand or perform activities of daily living. Hypoxic encephalopathy with Lance-Adams syndrome was assumed. Implementation of pharmacological treatment coupled with an intensive interdisciplinary rehabilitation program produced marked symptomatic and functional improvements which permitted autonomous activities of daily living and supervised locomotion after 7 months. The aim of this report was to emphasize the importance of the correct diagnosis and proper management of Lance-Adams syndrome leading to the improvement of the patients’ functional outcomes.

Keywords: Myoclonus/rehabilitation
**Introduction**

Survivors of cardiorespiratory arrest have a high incidence of neurological impairment due to anoxic brain injury. Accurate prognosis following these events is required to guide medical management and discussion with relatives.

Posthypoxic myoclonus is one of the characteristic findings and it can be divided in 2 types: acute posthypoxic myoclonus or myoclonic status epilepticus (MSE) and chronic posthypoxic myoclonus or Lance-Adams syndrome (LAS).

The first occurs usually within 12-24 hours after hypoxic brain injury (and is no longer present after 48 hours) and is characterised by spontaneous, repetitive, unremitting, generalised myoclonus involving the face, limbs and axial muscles in patients who are deeply comatose, carrying a poor prognosis.¹

LAS is characterized by action myoclonus occurring after a patient regains consciousness following successful cardiopulmonary resuscitation (CPR). It begins days to weeks after CPR and persists chronically. However, it can also develop acutely, which can easily lead to misdiagnosis.¹

LAS should be distinguished from MSE as the latter carries a poor prognosis while the former carries a more favourable one. The most important distinguishing feature between them is presence of coma, which is necessary for the diagnosis of MSE, while LAS patients are aware but it can be masked by deep sedation to control seizures.¹

LAS can be challenging to treat in a rehabilitation setting and it greatly impairs the patient’s functional ability and participation while increasing the burden on caregivers. Occurrence is rare with fewer than 200 cases reported in the literature.²

The authors report a case of successful rehabilitation of LAS.

**Case Report**

A 41-year-old male with medical history of squamous cell carcinoma of the penis, submitted in the past to partial amputation of the penis and bilateral inguinal and pelvic lymphadenectomy, under curative chemotherapy with paclitaxel, ifosfamide and cisplatin. Due to anemia, electrolyte disturbances and aggravating kidney function, the last treatment was administered in an inpatient setting.

On the 4th day, an episode of respiratory arrest occurred and after successful CPR he was placed in invasive mechanical ventilation. After two days, convulsive tonic-clonic seizures occurred (controlled with levetiracetam and phenytoin). Brain computer tomography (CT) and lumbar puncture did not show significant findings.

After being weaned off sedatives, he regained consciousness and presented with dysarthria, tetraplegia, ataxia, action and intention myoclonus which lead to the diagnosis of LAS. A 24 hours Holter, echocardiogram and magnetic resonance imaging (MRI) of the brain did not show abnormal findings.

Drug titration was performed with levetiracetam (100 mg tid), valproate (1000 mg qd + 500 mg bid), clonazepam (3 mg tid) with partial improvement of symptoms.

At discharge he was unable to assume a standing position or perform activities of daily living (ADL) due to severe myoclonus. For that reason, he was referred to our Physical Medicine and Rehabilitation (PMR) department where he was admitted as an inpatient 4.5 months after the event.

At admission he presented with cognitive impairment, mild dysarthria, moderate intention and action myoclonus in all limbs, mild global weakness - grade 4 in the Medical Research Council scale (MRC), mild appendicular ataxia (dysmetria <5 cm and tremor with an amplitude <2 cm in the finger chase and nose-finger tests, slightly abnormal heel-shin slide), marked dysdiadochokinesia, agaphria due to motor findings, effective seating with slight intermittent sway of the trunk, ineffective static standing balance with marked sway of the trunk and preference for bearing weight on the left lower limb (able to stand >10s only with constant support of one arm), ataxic gait only possible for very short distances (<5 m) with strong support of the examiner. Scale for the assessment and rating of ataxia (SARA): 21.

In the functional evaluation he showed need for minimal assistance for eating, dressing the lower body and transfers; need for supervision for grooming, dressing the upper body, bathing and toileting; need for total assistance for locomotion. Functional Independence Measure (FIM): 90 (motor score 56, cognitive score 34). Barthel index (BI): 60.

Dynamic computerized posturography (DCP) was performed at admission (Fig. 1): weight bearing/squat (WBS) test showed asymmetry with reduced weight bearing in the right lower limb (knee flexion 30º, 60º and 90º), modified clinical test of sensory interaction on balance (mCTSIB) showed increase in the mean center of pressure sway velocity in firm surface/eyes open, firm surface/eyes closed and foam/eyes open (“fall” in all 3 attempts in the latter), impossible to test in foam/eyes closed: impossible to perform any other test namely limits of stability (LOS) and sit-to-stand (STS).

A neuropsychological evaluation showed reduced verbal conceptualization, verbal initiative, work memory, visual memory, organization and sequencing.

The patient was inserted in an interdisciplinary rehabilitation program including medical, nursing, physiotherapy, occupational therapy, speech therapy, psychology and...
social care with the goals of improving ability for ADL and participation, motor control of the limbs and trunk, manual dexterity, balance, gait, speech articulation and cognition.

The rehabilitation program included:

- Two physical therapy sessions (60 minutes + 90 minutes), 5 days per week, consisting of: 30 minutes of initially light intensity aerobic exercise with the use of a static bicycle progressing to moderate intensity (in the 90-minute session); 15 minutes of active range-of-motion exercises for the trunk and limbs and stretching of the main muscle-tendon units; 20 minutes of dynamic muscle strengthening exercises of the main muscle groups of the limbs and core starting with closed-kinetic chain exercises and progressing to open-chain exercises with the use of dumbbells initially with light intensity; 25 minutes of coordination and balance training consisting of Frenkel exercises while lying down and progressing to sitting and standing positions, static balance exercises in quadruped, sitting and standing positions with bipedal support and with use of mirror visual feedback, progressing in difficulty with reduced upper limb support and varied foot positions to decrease base of support and with progressive utilization of somatosensory inputs (eyes closed) as well as visual and vestibular inputs (foam surface) and progressing to dynamic balance exercises (e.g. kneeling, sidesteps, application of external forces). With the favourable progress of the patient, assisted gait training was initiated in a smooth surface and in a straight line with progressive inclusion of direction changes and stair climbing with gradually less assistance.

- One 60-minute session of occupational therapy, 5 days per week, consisting of repetitive task-specific activities for the upper extremities emphasising reaching, ADL, manual dexterity and fine motor skills.

- One 30-minute session of speech therapy, 5 days per week, consisting of exercises for speech articulation and speech-respiration coordination.

- Daily transfer and ADL training by the nursing staff throughout the day (e.g. during dressing, personal hygiene, toileting and meals).

At discharge (7 months after the event) there was significant improvement in cognition, myoclonus, muscle strength (grade 5 MRC in all limbs), dysdiadochokinesia (slightly irregular movements), limb ataxia (no dysmetria, small tremor in the finger chase and nose-finger tests, slightly abnormal heel-shin slide), trunk ataxia and standing balance (able to stand with feet together >10s with some sway) and gait ataxia (considerable staggering with difficulties in half-turn but without support, tandem walking impossible). SARA: 10.

Figure 1 - DCP at admission.
Figure 2 - DCP at discharge.
He showed modified independence for all ADL except needing supervision for walking and stair climbing. FIM: 112 (motor 78, cognitive 34). BI: 90.

DCP at discharge (Figure 2) showed: no asymmetry in WBS, mCTSIB still showed increase in mean center of pressure sway velocity but marked improvement with firm surface/eyes closed and foam/eyes open, LOS was now possible to perform showing decreased endpoint and maximum excursions and decreased directional control in all directions but especially to the right and back and decreased movement velocity to the right and back. StS was also now possible to perform, being within normal parameters except for slightly reduced bodyweight rising index (force applied by lower limbs during sit-to-stand).

Follow-up after discharge was not possible as the patient returned to his area of residence, resuming PMR treatments and follow-up locally as well as maintaining follow-up by Urology and Oncology at his local hospital.

Discussion

LAS is characterized by action or intention myoclonus (typically triggered by startle and tactile stimulation, disappears with relaxation/sleep and is more marked for precise movements/tasks). Cerebellar dysfunction (dysarthria, ataxia, intention tremor) is usually present further impairing coordination, balance and function. It can be associated with negative myoclonus (abrupt lapses in tone in antigravity muscles) which can additionally impair gait and lead to falls. Seizures and mild cognitive deficits may also be observed.3,4

Our patient developed action myoclonus, ataxia, dysarthria and mild cognitive anomalies after regaining consciousness following an episode of respiratory arrest while the onset was preceded by seizure. This clinical picture fulfilled the criteria for LAS.

As previously stated, the prognosis is quite different between acute and chronic posthypoxic myoclonus. MSE is associated with poor outcome while LAS has a good prognosis and is associated with survival with or without chronic myoclonus and cerebellar dysfunction.1

The functional prognosis of LAS varies among published cases but it seems to carry a high functional impairment.

Post-mortem studies have documented widespread ischaemic brain injury in MSE.1

A post-mortem study in LAS has shown neuronal loss in the thalamus, striatum, mammillary bodies and brainstem raphe nuclei.5 Thus, there is diffuse damage but distinguishing pathoanatomic changes are yet to be defined.

LAS is more commonly associated with respiratory arrest than primary cardiac arrest.2,3,6

When cardiac arrest occurs it is usually hypoxic rather than circulatory. In LAS there is typically a documented period of hypoxia preceding hypoxic cardiac arrest.1

The metabolic changes resulting from the period of severe hypoxia are thought to modify the cerebral lesion. Pure hypoxic events seem to have better outcomes than those with circulatory arrest. Several factors have been suggested and it’s likely that hypoxic preconditioning involves many different substances.7

Our patient had respiratory arrest without cardiac arrest which may have contributed to the better outcome.

LAS has varied neurochemical anomalies.

Levels of 5-hydroxyindoleacetic acid, the primary metabolite of serotonin, have been shown to be reduced in cerebrospinal fluid of LAS patients. This finding, coupled with the improvements that can be achieved by administration of 5-hydroxytryptophan (5-HTP), the immediate precursor of serotonin, suggests a role for low serotonin levels in the disease process.8

Gamma-aminobutyric acid (GABA) may also be involved, interacting with the serotonin system to suppress posthypoxic myoclonus.9

Welsh et al10 proposed that myoclonus after brain anoxia starts with the death of Purkinje cells at the cerebellar fastigial nucleus. The resultant loss of GABAergic inhibition leads to diaschisis of the motor thalamus and reticular formation of the medulla leading to increased motor excitability.

Imaging tests, such as CT and MRI, have not demonstrated findings that are diagnostic of LAS.11,12

Our patient’s CT and MRI had no abnormalities.

Recent use of brain 18F-fluorodeoxyglucose with single-photon emission computed tomography (SPECT) and positron emission tomography (PET) has helped to elucidate the pathoanatomical base of LAS.

One study reported PET findings of bilateral increased glucose metabolism in the pontine tegmentum, mesencephalon and ventrolateral thalamus in 7 patients with LAS compared with 10 controls.13

SPECT has shown decreased perfusion in the basal ganglia, frontal lobe, parietal lobe, and the left temporal lobe in LAS cases.4,12,14
There is also no consistent correlation with electroencephalogram (EEG) abnormalities.

A recent review showed epileptiform activity in up to two thirds of cases.

A retrospective study described vertex-localized spike-waves in 12% of patients, of whom 50% survived with favourable outcomes and were subsequently diagnosed with LAS. These findings localize the phenomenon to the motor cortex.

Of those undergoing electroencephalogram-electromyography (EEG-EMG) polygraphy, about 60% demonstrated jerk-locking, signifying cortical myoclonus, which was further demonstrated by the presence of “giant” somatosensory evoked potentials.

Due to the incomplete understanding of the pathophysiology of LAS, its ideal treatment has not been established. A combination of drug regimens based on the hypothesis of neurotransmitter deficiencies has been reported.

5-HTP or oxitriptan, (available in Portugal in 100 mg capsules) may have a beneficial effect as its administration seems to increase 5-hydroxyindoleacetic acid, a metabolite of serotonin, in the cerebrospinal fluid, although the appropriate dosage has not been established.

Valproate has been shown to be beneficial with its likely mechanism being elevation of GABA in synaptic regions.

Clonazepam has also shown to be effective with its possible mechanism being facilitation of GABAergic transmission and decrease in 5-hydroxytryptophan utilization in the brain.

A review of 122 cases showed significant or full improvement in 51% of the 47 patients on clonazepam, 40% of the 43 patients on 5-HTP, 45% of the 22 patients on valproic acid and 50% of the 6 patients on piracetam. Often multiple medications were needed and the authors recommended a combination of valproate and clonazepam as first-line therapy, with 5-HTP in resistant cases.

Several groups have confirmed the efficacy of levetiracetam in posthypoxic myoclonus.

In a more recent review, levetiracetam was recommended as first line-treatment, zonisamide, clonazepam, and valproate as secondary-line agents, and 5-HTP in resistant cases.

Our patient was treated with levetiracetam, valproate and clonazepam which were effective in controlling myoclonus and did not produce significant sedative effects.

Based on findings of hypermetabolism in the ventrolateral thalamus on PET, stereotactic targeting of the ventrolateral thalamus using deep brain stimulation has been suggested for patients with severe, and refractory posthypoxic myoclonus.

Deep brain stimulation surgery targeting the globus pallidus internus, although still experimental, has been performed in some refractory cases with initial encouraging results.

Intrathecal baclofen has been shown to improve myoclonus in a refractory case of LAS.

In conclusion, it is important to distinguish between MSE and LAS owing to their different pathophysiology and prognosis, the key feature being the presence/absence of coma. Early and accurate diagnosis of LAS can prevent the delay of treatment. As this case illustrates, an appropriate pharmacological and rehabilitation regimen may lead to good functional outcomes. Hopefully, as the knowledge about the mechanisms behind LAS increases more effective treatments may emerge.

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