

# Lance-Adams syndrome in a patient with congenital coagulation factor XIII deficiency and spontaneous atypical subdural hematoma: case report

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**ABSTRACT** – Lance-Adams syndrome, first described in 1963, is a condition characterized by development of chronic post-hypoxic action myoclonus due to a temporary lack of or inadequate brain oxygen supply. A coagulation disorder should be suspected when an unexplained hemorrhage occurs. Patients with Lance-Adams syndrome show favorable response to sodium valproate and clonazepam. A case is presented of a 22-year-old man admitted to University Department of Neurology, Zagreb University Hospital Center, in January 2008. Clinically, the patient presented with headache, nausea, vomiting, mild right hemiparesis and truncal ataxia. Brain magnetic resonance revealed spontaneous atypical subdural hematoma in the region of the right middle cerebellar peduncle, vermis and left cerebellar hemisphere. Laboratory findings revealed coagulation factor XIII deficiency. Two weeks of admission, the patient developed spontaneous subdural hematoma in the right frontoparietal region. In the meantime, clinically he also developed generalized action myoclonus that was, according to our belief, a part of chronic post-hypoxic action myoclonus, i.e. Lance-Adams syndrome (secondary to intracranial hemorrhage). Oral administration of sodium valproate and

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clonazepam, and replacement therapy for normalization of coagulation factor XIII concentration resulted in complete regression of myoclonus.

**Key words:** Lance-Adams syndrome, post-hypoxic myoclonus, coagulation factor XIII, spontaneous subdural hematoma

## INTRODUCTION

Two types of post-hypoxic myoclonus (PHM), i.e. acute and chronic ones, can occur in patients with hypoxic injury of the brain. Acute PHM, or so-called post-hypoxic myoclonic status epilepticus (MSE), occurs soon after a hypoxic insult and is characterized by generalized myoclonic jerks in patients who are deeply comatose, which implies a poor prognosis (9). Chronic PHM, also known as Lance-Adams syndrome (LAS), first described in 1963, is a condition characterized by development of chronic post-hypoxic action myoclonus due to a temporary lack of or inadequate brain oxygen supply. Clinical presentation is action myoclonus associated with cerebellar ataxia, postural imbalance, and very mild intellectual deficit. The occurrence of Lance-Adams syndrome is rare; 122 cases have been reported in the literature so far. Histopathologically, there are structural changes, i.e. prominent astrocytosis in nuclei of the mesencephalic gray matter, loss of neurons, and changes in the periaqueductal gray matter of the brainstem and dorsolateral gray matter of mesencephalic tegmentum (3<sup>rd</sup> mediator system of epileptogenesis). The generator of myoclonus is the caudal part of medulla oblongata and upper part of cervical spinal cord, as well as cerebral cortex (7,11). Patients with LAS show favorable response to sodium valproate and clonazepam (12).

A coagulation disorder should be suspected when an unexplained hemorrhage occurs. The incidence of Factor XIII deficiency is estimated at one *per* five million births. It is inherited as an autosomal recessive disorder, which means that it affects men and women equally. Congenital coagulation factor XIII deficiency can be a possible cause of unexplained intracranial hemorrhages in young adults. Ongoing factor replacement therapy is recommended to prevent further bleeding episodes.

## CASE REPORT

A case is presented of a 22-year-old man admitted to University Department of Neurology, Zagreb University Hospital Center, in January 2008. Clini-

cally, the patient presented with headache, nausea, vomiting, mild right hemiparesis and truncal ataxia. Magnetic resonance imaging (MRI) of the brain revealed spontaneous atypical subdural hematoma in the region of the right middle cerebellar peduncle, vermis and left cerebellar hemisphere (Fig. 1). Cerebral digital subtraction angiography was negative.

Laboratory findings indicated probable congenital coagulation factor XIII deficiency. Two weeks after admission, the patient developed spontaneous subdural hematoma in the right frontoparietal region. In the meantime, clinically he also presented generalized action myoclonus that was, according to our belief, a part of chronic post-hypoxic action myoclonus, i.e. Lance-Adams syndrome (secondary to intracranial hemorrhage). Electroencephalography (EEG) showed polyspikes and a complex of polyspikes and slow waves, clinically synchronized with myoclonus (Fig. 2).

Oral administration of sodium valproate and clonazepam, and normalization of coagulation factor XIII concentration with replacement therapy re-

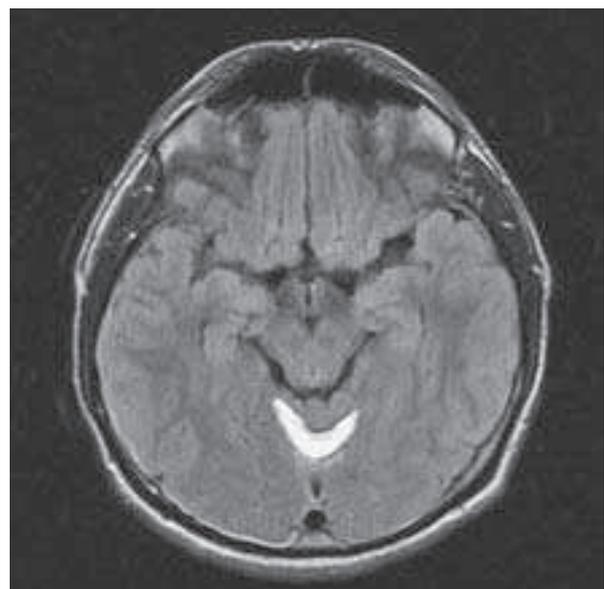


Fig. 1. Brain MRI of our 22-year-old patient revealing spontaneous atypical subdural hematoma in the region of the right middle cerebellar peduncle, vermis and left cerebellar hemisphere.

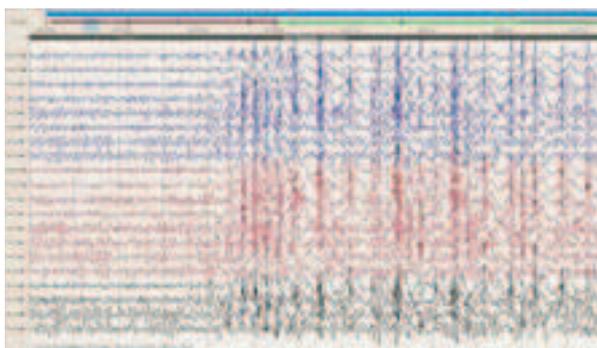


Fig. 2. EEG in our patient showing generalized polyspikes and slow waves, synchronized with myoclonus.

sulted in complete regression of myoclonus. His neurological status also improved.

## DISCUSSION

Myoclonus refers to sudden, shock-like, involuntary body movements that can occur in various patterns, i.e. focal, multifocal, or generalized. Chronic PHM, also known as LAS, is predominantly characterized by action myoclonus that has no consistent correlation with EEG abnormalities. LAS occurs in patients after they have regained consciousness days to weeks of cardiopulmonary resuscitation. Myoclonic jerks are specifically triggered by action, startle, and tactile stimulation, and they usually disappear with relaxation of the body and limbs or with sleep. The severity of myoclonus is proportional to the precision of the task that is required. Our patient developed generalized myoclonus accompanied by cerebellar ataxia two weeks of admission because of spontaneous atypical subdural hematoma in the region of the right middle cerebellar peduncle, vermis and left cerebellar hemisphere, and spontaneous subdural hematoma in the right frontoparietal region.

Clonazepam was found to have dramatic effects on PHM (12). Welsh *et al.* found that Purkinje cells were not uniformly sensitive to transient ischemia, but those located in the paravermal and vermal areas died most frequently. These cells project mainly to the ventrolateral thalamic nucleus but are deficient in aldolase C and EAAT4 (Excitatory Amino Acid Transporter 4), which is necessary to survive the pathologically intense synaptic input from the inferior olive after the restoration of blood flow (10,11). The authors considered that certain brainstem structures, the paravermal and vermal areas of the cerebellum, and the diencephalon may be implicated in human PHM. The loss of GABAergic

inhibition in cerebellar afferent neurons after ischemia leads to diaschisis of the motor thalamus and reticular formation, which, in turn, is responsible for enhanced motor excitability and myoclonus.

While the treatment for LAS is limited mainly due to the as yet obscure pathophysiological mechanisms involved, LAS has an excellent prognosis if treated early (11,12). A combination of medications based on the neurotransmitter hypotheses is often needed to obtain appropriate control of symptoms. Frucht and Fahn (3-5) reviewed more than 100 cases of LAS and found that clonazepam, sodium valproate, and piracetam were significantly effective in approximately 50% of patients. Recently, several groups have confirmed the efficacy of levetiracetam in PHM (4). Clonazepam, sodium valproate, piracetam, and levetiracetam may be recommended as first-line agents to treat patients with LAS. A combination of medications including clonazepam and sodium valproate provided good control of myoclonus in our patient, whereas a previously reported Chinese LAS case was effectively treated with 5-hydroxytryptophan, fluoxetine hydrochloride and carbidopa tablets (6).

Congenital coagulation factor XIII deficiency could be the possible cause of unexplained intracranial hemorrhages in young adults (1,2).

Our patient had congenital coagulation factor XIII deficiency. Coagulation factor XIII replacement therapy and oral administration of sodium valproate and clonazepam led to complete resolution of myoclonus. His neurological status also improved.

## CONCLUSION

A coagulation disorder should be suspected when an unexplained intracranial hemorrhage occurs. The incidence of Factor XIII deficiency is estimated at one *per* five million births, and is inherited in an autosomal recessive pattern. Congenital coagulation factor XIII deficiency might be the cause of unexplained intracranial hemorrhages in young adults. Ongoing factor replacement therapy is recommended to prevent further bleeding episodes. The authors indicate the importance of accurate diagnosis and appropriate treatment.

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## Lance-Adamsov sindrom kod bolesnika s kongenitalnim deficitom koagulacijskog faktora XIII i spontanom atipičnim subduralnim hematomom: prikaz bolesnika

**SAŽETAK** - Lance-Adamsov sindrom prvi put je opisan 1963. godine kao stanje obilježeno razvojem kroničnog post-hipoksijskog akcijskog mioklonusa nastalog zbog privremenog gubitka kisika ili nedostatne opskrbljenosti mozga kisikom. Kod neobjašnjivih krvarenja uvijek postoji sumnja na poremećaj koagulacije. Prikazuje se slučaj 22-godišnjeg bolesnika koji je hospitaliziran u Klinici za neurologiju, KBC Zagreb u siječnju 2008. godine zbog glavobolje, mučnine, povraćanja, blage desne hemipareze i trunkalne ataksije. Magnetskom rezonancom mozga dokazan je atipični subduralni hematoma u području desnog cerebelarnog pedunkula, vermisa i lijeve cerebelarne hemisfere. Laboratorijski nalazi su ukazali na deficit faktora koagulacije XIII. Dva tjedna nakon hospitalizacije kod bolesnika je došlo do razvoja spontanog subduralnog hematoma i u desnoj frontoparijetalnoj regiji. U međuvremenu je u bolesnika došlo do razvoja generaliziranog akcijskog mioklonusa, odnosno kroničnog post-hipoksijskog akcijskog mioklonusa, tj. Lance-Adamsova sindroma (kao posljedica intrakranijskog krvarenja). Nakon peroralne terapije valproatima i klonazepamom te nadoknade faktora XIII i njegove normalizacije u krvi došlo je do potpune regresije mioklonusa.

**Ključne riječi:** Lance-Adamsov sindrom, post-hipoksijski mioklonus, koagulacijski faktor XIII, spontani subduralni hematoma