Peripheral neuropathy as a complication of diabetic ketoacidosis in a child with newly diagnosed diabetes type 1 – a case report

Short Running Title: Peripheral neuropathy after diabetic ketoacidosis

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What is already known on this topic: Neurological complications of ketoacidosis in diabetes mellitus type 1 are serious clinical problems. Neuropathy after ketoacidosis in children is extremely rare. There are described only few cases of this complication.

What this study adds: This paper presents the current state of knowledge about peripheral neuropathy in pediatric patients with new onset diabetes type 1. It includes clinical presentation, pathophysiology and available treatment for this rare complication.

Abstract:
BACKGROUND: Neurological complications of diabetic ketoacidosis are considered to be very serious clinical problem. The most common complication is cerebral edema. However this group includes also less common syndromes such as ischemic or hemorrhagic stroke, cerebral venous and sinus thrombosis or very rare peripheral neuropathy.
CASE REPORT: We present a case of 9-year-old girl with new onset type 1 diabetes, diabetic ketoacidosis, cerebral edema, multifocal vasogenic brain lesions and lower limbs peripheral paresis. The patient developed polydipsia and polyuria one week before admission to the hospital. In laboratory tests initial blood glucose level 1136 mg/dl and acidosis (pH 7.1; BE -25.9) were noted. She was admitted to the hospital in a critical condition and required treatment in intensive care unit. Computed tomography scan showed brain edema and hypodense lesion in the left temporal region. Brain MRI revealed more advanced multifocal brain lesions Nerve conduction studies demonstrated damage of the motor neuron in both lower extremities with dysfunction in both peroneal nerves and the right tibial nerve. As a result of diabetological, neurological treatment and physiotherapy patient’s health state gradually improved.
CONCLUSIONS: Acute neuropathy after ketoacidosis is rare complication and its pathomechanism is not clear. Patients with DKA require careful monitoring of neurological functions even after normalization of glycemic parameters.

Keywords: polineuropathy, ketoacidosis, diabetes mellitus type 1, children.

Background
Neurological complications of ketoacidosis in diabetes mellitus type 1 (DM1) are serious clinical problem. Brain edema is the most common CNS complication which occurs in approximately 0,5-1% DKA cases with 20% mortality rate (1,2). Ischemic and hemorrhagic strokes are less common and account for 10% of intracerebral complications of DKA (3). Brain vein and sinus thrombosis are less frequent and neuropathy after DKA is extremely rare.

Case report
We present a case of 9-year-old girl with newly diagnosed DM1, DKA, brain edema, multifocal vasogenic brain lesions and lower limb paresis. A week of polyuria, polydipsia, and 3 kg of weight loss over the previous month were observed. The patient was admitted to the district hospital in a serious clinical condition with severe dehydration.
Initial intravenous fluid therapy included infusion of 15 mL/kg of 0.9% sodium chloride during first 90 minutes. The total volume of fluids which were administered during first 12 hours was 65 mL/kg (patient’s weight - 34.6 kg): 1250 mL 0.9% NaCl and 1000 mL of 5% dextrose with 0.9% NaCl (2:1 proportion, sodium concentration - 51.34 mEq/L). Intravenous insulin therapy was introduced with initial dose 0.05 units/kg/hour in order to prevent the rapid decrease of glycaemia. After 3 hours the patient’s medical state and neurological condition deteriorated. She experienced motor restlessness and agitation followed by the upper limbs spasms. At the end of the 1st day of treatment the patient was referred to the Intensive Care Unit of the Children’s Memorial Health Institute (ICU) with Glasgow Coma Scale (GCS) score of 13 points. Laboratory tests are shown in Table 1.

After 6 hours from admission to the ICU the clinical state was rapidly deteriorating and GCS score decreased to 7 points. CT scan revealed brain edema and 13 mm hipodense lesion in the left temporal region (Fig. 1).

The patient was sedated and intubated. Insulin infusion was continued and intravenous fluid administration was diminished. Anti-edematous treatment was introduced (Mannitol 0.3 g/kg/dose 3 times/day). Patient’s medical state was gradually improving. After 4 days she was extubated. Subsequently the patient was transferred to the Department of Endocrinology and Diabetology. Despite improvement in clinical condition the girl was suffering from symmetric foot paresis. Brain MRI revealed numerous, diffuse lesions (Fig. 2, Fig. 3).

Subsequently cerebral spinal fluid was tested. On the basis of the laboratory tests infection and neoplasm of CSN were ruled out.

Lower limbs nerve conduction studies (NCS) revealed the damage to the motor neuron in both lower extremities with dysfunction in both peroneal nerves and in the right tibial nerve. According to neurologists the etiology of multifocal brain lesions was vasogenic, however the cause of neuropathy was not fully clear. They indicated that DKA and peripheral ischemia were probably the ground for its development.

Alpha lipoic acid and vitamin B1, B6, B12 were introduced and the patient underwent intensive physiotherapy which led to improvement of left lower limb motor function.

Brain MRI was performed 3 months later in which no progression in size and number of the brain lesions was observed. NCS revealed normalization of the left peroneal nerve parameters. However substantial, persistent features of deep motor neuropathy of the right lower limb were still present.

**Discussion**

Diabetic neuropathy (DN) refers to the presence of symptoms and/or signs of peripheral nerve dysfunction due to diabetes. In order to diagnose this type of neuropathy different causes, such as vitamin deficiency, infection, inflammatory, toxic, autoimmune, paraneoplastic and genetic should be excluded (4). Neuropathy is the most common complication of diabetes in overall and can be seen in approximately 45% patients with DM2 and 54-59% patients with DM1 (5). Due to different symptoms, clinical courses and pathomechanism, diabetic neuropathy is categorized as a heterogenic group which includes many types of nerve dysfunctions. More than 80% of patients with symptomatic DN suffer from generalized symmetric, chronic polynuropathy including motor, sensory and/or autonomic nerve dysfunctions. In most cases DN develops on a basis of a long standing hyperglycemia and it takes years to develop (6). Symptomatic acute neuropathy which occurs with new onset DM1 is extremely rare and there is still little medical data on this issue (7). It is interesting that at the time of DM1 diagnosis asymptomatic changes in nerve function can be seen. Lee et al. (8) examined nerve conduction in children with newly diagnosed DM1 and periodically during their 5-year follow-up. This prospective study included patients aged 3-19 years old (n=37), who underwent bilateral NCS of median, ulnar, posterior tibial, peroneal, and sural nerves annually for 5 years. In 32.4% patients the examination revealed electrophysiological evidence of polyneuropathy in at least two different nerves at the diagnosis of DM1.

There are described few types of neuropathy related to newly diagnose DM1 – acute painful diabetic neuropathy, hyperglycemcic neuropathy and neuropathy after ketoacidosis. Dayal et al. (9) presented a case report of 12-year-old girl, who developed acute asymmetric sensorimotor neuropathy during the first month after diagnosis of DM1. In this period of time the authors observed reduction of HbA1c from 14.2% to 10.4% which was described as a potential trigger factor for neuropathy. Wilson et al. (10) presented similar case of DN. A 14-year-old boy was diagnosed with DM1. After 9 weeks of diabetes treatment the authors observed HbA1c level reduction
from 14.1% to 7.6%. These 2 cases present clinical features of acute painful diabetic neuropathy (APCN) also known as a treatment induced neuropathy (insulin neuritis). It is reversible disorder and affects patients with rapid improvement of diabetes metabolic control and has a favorable clinical outcome (11). In our case HbA1c level at DM1 diagnosis was 11.5% and one month later it was 9.6%. However this reduction doesn’t seem to confirm this type of neuropathy.

Another type of DN is hyperglycemic neuropathy. Its clinical presentation includes temporary limb hyperalgesia which is potentially reversible after glycemic normalization (12).

Rangel et al. (7) described a case of 10-year-old patient with new onset DM1 and concomitant acute mononeuropathy which manifested in difficulties in flexing the right foot and hyperalgesia in the dorsum of the right feet to the ankle. According to authors DM was the ground for this mononeuropathy as its onset was simultaneous with the onset of DM1. Motor dysfunction rapidly improved after adequate glycemic control.

Our patient suffered from acute motor peripheral neuropathy, occurrence of which was probably caused by DKA. This neuropathy can be a consequence of peripheral ischemia or hemodynamic and metabolic changes during ketoacidosis (13). One hypothesis is that the procoagulant state which occurs during DKA can cause nerve damage through vascular endothelial dysfunction, which is the first line of defense against thrombosis. Endothelium damage also leads to platelet and coagulation factors activation (14,15). The plasma levels of fibrinogen, VII, VIII, XI, XII and von Willebrand factor during DKA are elevated. Procoagulant state is enhanced by anticoagulant mechanisms disruption e.g. lowered protein C level. Fibrynolisis is also impaired due to different, more difficult to degrade structure of thrombi as well as the increased concentration of the plasminogen activator inhibitor type 1 (PAI-1) (14,15). The patient in our report had slightly elevated d-dimer’s level, however further diagnostic test were not carried out.

In our case other etiologies of neuropathy were taken into consideration like hypophosphatemia which was observed during admission to the district hospital. Hypophosphatemia is generally asymptomatic. Nonetheless its severe form (<0.32 mmol/l) can lead to peripheral polyneuropathy which may be both motor and sensory (16). However in our case neurological symptoms were present even after phosphate normalization. Differential diagnosis included also Guillian-Barre syndrome, but no typical pathology in cerebrospinal fluid was detected.

The treatment of diabetic neuropathy includes either causative or symptomatic therapy. Causative methods include usage of strong antioxidants such as alpha lipoic acid. Its effectiveness was proven in meta-analyses (17, 18). Derivative of vitamin B1 – benfotiamine increases the utilization of active glycolysis products. However it is less effective than alpha lipoic acid (19). Symptomatic treatment includes painkillers, antiepileptics and antidepressants.

Conclusions
Neuropathy is not only seen as late complication of diabetes mellitus, it can develop anytime after DM1 diagnosis (6). Acute neuropathy after ketoacidosis is rare complication and its pathomechanism is not clear. Patients with DKA require careful monitoring of neurological functions for at least 48 hours after normalization of glycemic parameters (20).

Informed Consent: Written consent was obtained from the patient’s parents.

Authorship Contribution:

Financial Disclosure: The authors declared that this study received no financial support.

References

Table 1. Results of laboratory tests during admission to the district hospital and ICU

<table>
<thead>
<tr>
<th>Parameters</th>
<th>District Hospital</th>
<th>Intensive Care Unit of the Children’s Memorial Health Institute</th>
<th>Reference ranges</th>
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<td>Glucose (mg/dl)</td>
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<td>308</td>
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<td>Osmolarity</td>
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<tr>
<td>Parameter</td>
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<td>Normal Range</td>
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<td>-----------------------------------</td>
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<td>----------------------</td>
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<tr>
<td>(mOsm/kg H2O)</td>
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<td>D-dimer (ug/l)</td>
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<tr>
<td>Fibrinogen (g/l)</td>
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<td>1.9-3.6</td>
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</table>

**Fig. 1.** Brain CT scan: 13 mm hypodense lesion in the left temporal lobe, not visible after contrast injection – ischemic lesion? The supratentorial ventricular system is narrow and symmetrical. Cerebral sulci are effaced.
Fig 2. Brain MRI. T1-weighted scan. Lesions located in the corpus callosum and the midbrain.

Fig 3. Brain MRI. FLAIR sequence. Lesions located in the medial parts of the temporal lobes and in the lower-medial area of the frontal lobes and the ventricles.