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Case report

Coexistence of type 1 diabetes mellitus and spinal muscular atrophy in an 8-year-old girl: a case report

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The spinal muscular atrophy is a rare autosomal recessive genetic disease characterized by the progressive loss of muscular strength. In its natural course the disease leads to death. Diabetes mellitus type 1 is an autoimmune metabolic disorder characterized by the disturbed insulin synthesis. This is a case report of an 8-year-old girl suffering from Werdnig Hoffman disease in whom DM1 was diagnosed. The unspecific clinical manifestation and diagnostic difficulties are presented in this paper. To the authors' knowledge, this is the first publication concerning the co-existence of these two medical conditions.

Key words: Spinal muscular atrophy, diabetes mellitus, children

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INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disease linked to a mutation in the survival motor neuron 1 gene (*SMN*1) (Lunn *et al.,* 2008).

The prevalence of this disease is estimated as being one in 10 000 live births and the carrier frequency as 1 in 50. The disease is characterized by a progressive muscular atrophy caused by the degeneration of motoneurons in spinal cord and cranial nerves (Lunn *et al.,* 2008).

The clinical manifestation of SMA is diversified. The first symptoms may occur in infancy (type I, Werdnig-Hoffmann disease), in childhood (type II and III) or in adulthood (type IV) (Lunn *et al.,* 2008). The main characteristic of SMA is a progressive loss of muscle strength and generalized muscular hypotonia, leading to immobilization, swallowing difficulties, breathing disorders and eventually respiratory insufficiency (Lunn *et al.,* 2008).

The diagnosis of SMA is based on medical history, physical examination, electromyography and muscle biopsy confirmed by the molecular identification (Lunn *et al.,* 2008).

There is no cure for SMA and the natural outcome of this disease is death. However, in recent years the prognosis for life expectancy has improved. It may be attributed to the combined treatment of respiratory failure (including respiratory therapy), nutritional support (i.e. enteral nutrition), orthopedic and surgery procedures (Wang *et al.,* 2007).

Diabetes mellitus is a metabolic disease, characterized by the disturbed insulin synthesis and/or ineffective insulin response, resulting in hyperglycemia (Craig *at al.*, 2009). According to the pathomechanism, there are 4 types of the disease distinguished.

The pathogenesis of DM1 is due to the destruction of beta cells in pancreatic islets. This is an immune-mediated process in which lymphocytes T are engaged. In 85–90% of the patients serological markers such as insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD) and protein tyrosin phosphatase (IA-2 IA-2B) are present (Craig *at al.*, 2009; Daneman, 2006). Viral infections with enterovirus, Coxackie or Rubella are considered to play some role in DM etiology (Craig *at al.,* 2009).

One presumes that the presence of *IDDM* gene (insulin-dependent diabetes mellitus) predisposes a person to diabetes. So far, some of these genes have been identified: *IDDM*1 — 6p21-31, *IDDM*2 11p15-5 as well as *IDDM*12 2q33 (Daneman, 2006).

The clinical manifestation of DM1 includes: poliuria, polidypsia, weight loss, nycturia, enuresis, lethargy, fatigue, abdominal pain and vision changes. Some of these symptoms may initially be ignored. Thus, the diagnosis may be delayed and the disease recognized as late as severe life-threatening symptoms (such as diabetic ketoacidosis with a coma or, rarely, hyperglycemic hyperosmolar nonketotic syndrome) occur (Craig *at al.,* 2009; Daneman, 2006).

Since DM1 is recognized as an autoimmune process, the patients may also suffer from other autoimmune diseases, e.g. Hashimoto's thyroiditis, Grave's disease, Addison's disease, celiac disease, myastenia gravis, virtiligo and others (Daneman, 2006).

DM is confirmed by a high plasma glucose concentration (fasting glucose level $\geq$ 7.0 mmol/L (126 mg/dL); plasma glucose $\geq$11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test) or random blood glucose $\geq$11.1 mmol/L (200 mg/dL) (Craig *at al.*, 2009).

The aim of DM1 therapy is to sustain euglycemia. The management consists of: insulin therapy, appropriate diet and exercise.

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Abbreviations: DM, diabetes mellitus; GAD, glutamic acid decarboxylase; IAA, insulin autoantibodies; IDDM, insulin-dependent diabetes mellitus; NAIP, neuronal apoptosis inhibitory protein; SMA, Spinal Muscular Atrophy; SMN, survival motor neuron; TGA, transglutaminase antibodies; TgAb, thyroglobulin antibodies; TPO, anti thyroperoxidase antibodies

The aim of this study was to report the case of DM1 in an 8-year-old girl with SMA type I.

CASE REPORT

The 8-year-old girl, suffering from SMA (Werdnig Hoffman disease) was admitted to hospital with the symptoms of disorders of consciousness, fever and coffee ground content in stomach (found after aspiration via gastrostomy). Medical history revealed that for the few weeks preceding the admission, the girl had been agitated with tachycardia and fever, initially accompanied with gingivitis. The latter receded but other disorders occurred: coffee ground stomach content, rare miction with urinary retention (palpable bladder in physical examination). The girl was born in 40 Hbd, birth weight 3.81 kg, 9 pts Apgar.

SMA was diagnosed at the age of 5 months, confirmed with genetic testing. Deletion of exons 7 and 8 in *SMN* (survival of motoneuron) gene and deletion of exons 5 and 6 in *NAIP* (neuronal apoptosis inhibitory protein) gene were identified. Three months later (at the age of 8 months), respirathorotherapy was initiated and a gastrostomy tube was inserted.

Before the current hospitalization, the girl had been nourished *via* gastrostomy with commercially prepared complete, normocaloric enteral formulas (500 ml Nutrison/Nutricia and 250 ml Nutrison Multi Fibre/Nutricia) combined with homemade mixed food (250 ml). The total amount of fluids was 1 500–2 500 ml, depending on season.

Medical family history concerning autoimmune diseases was negative.

On admission, the child's general condition was estimated as severe. The examination revealed: somnolence, respiratory insufficiency (mechanical ventilation), generalized muscle hypotonia, tachycardia, dehydration and peripheral cyanosis.

Abnormal laboratory findings were as follows: hyperglycemia 27.7 mmol/L (500 mg/dL), metabolic acidosis, hypernatremia (151 mmol/l), low C-peptide level (0.26 ng/ml/norm: 0.9–7.1ng/ml) and glycosylated hemoglobin HbA1C level as high as 12.44 (norm < 5).

Serological biomarkers — anty glutamic acid decarboxylase antibodies, transglutaminase antibodies (TGA), anti thyroperoxidase antibodies (TPO) or thyroglobulin antibodies (TgAb) were not present.

DM1 was diagnosed and intensive treatment was initiated: intravenous re-hydration and insulin therapy (initially continuously) after which clinical improvement and normoglycemia were achieved.

Presently, a year after the DM was diagnosed, the girl is treated with: continuous respirathorotherapy, NPH-insulin once a day (Insulatard/Novo Nordisk 6 units), short-acting insulin 3 times a day (Actrapid/Novo Nordisk 4.5/2.5/3.5 units), and nutritional treatment via gastrostomy tube (Nutrison, Nutrison Multi fibre 750 ml/day plus homemade diet). Plasma glucose level ranges 3.8–8.3 mol/l (70–150 mg/dl); glycosylated hemoglobin level is between 5 and 6%.

DISCUSSION

The incidence of SMA is quite constant (Lunn *et al.,* 2008), but the prevalence of DM1 increases, however it varies in different countries — the highest is observed in Finland, Sweden and UK, the lowest in the East (China, Japan, Korea). It must be noted that recently DM1 is more often diagnosed in younger children; in 50–60% the disease onset is at the age of 16–18 years. In Poland, it is assumed that the incidence is 10–15 per 100 000 children at the age of 0–14 years (Daneman, 2006).

Both SMA and DM1 are relatively rare diseases and the probability of their co-existence is very low. However, due to the development of medicine, e.g. availability of artificial ventilation, life expectancy of patients with SMA improves. In such circumstances it could be expected that these two rare diseases (both SMA and DM1) might be diagnosed in one individual more often.

To the authors' knowledge, this is the first publication concerning such a case.

The recognition of any complaints in children with severe advanced SMA, using mechanical ventilation, is usually very challenging for both parents and doctors. The main obstacle is a limited contact with the patient. Lethargy, apathy and peritoneal signs are difficult to evaluate in a child who cannot speak, does not move, manifests generalized muscular hypotonia and ptosis (due to muscle atrophy).

In the patient described in this paper, the objective symptoms of the ongoing disease and/or worsening of the general condition such as digestive disorders and hemorrhaging from the digestive tract were present. It may be assumed that tachycardia additionally epitomized the pain and/or dehydration. However, this is a very nonspecific symptom. It must be noted that instead of typical symptoms such as polydypsia, poliuria, urine retention and rare mictions were recorded. This phenomenon is difficult to explain. Due to the main disease (SMA) and gastrostomy feeding by the parent, the girl could not drink as much as she probably wished. The authors consider that muscle hypotonia is responsible for the bladder distention. Nevertheless, rare mictions are not fully understood.

The proper diagnosis was based on laboratory tests. This enabled the initiation of adequate treatment with good results.

CONCLUSION

The incidence of SMA and DM1 coexistence is very rare.

The diagnosis of a life-threatening condition in a mechanically ventilated patient with severe advanced SMA is difficult, because the patient cannot articulate his or her complaints.

In severely and chronically ill patients, new pathological symptoms should initiate a differential diagnosis of another, coexisting disease.

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