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Brief Report

Diabetes mellitus in Friedreich Ataxia: A case series of 19 patients from the German-Austrian diabetes mellitus registry

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ABSTRACT

Friedreich ataxia (FRDA) is a multisystem autosomal recessive disease with progressive clinical course involving the neuromuscular and endocrine system. Diabetes mellitus (DM) is one typical non-neurological manifestation, caused by beta cell failure and insulin resistance. Because of its rarity, knowledge on DM in FRDA is limited.

Based on data from 200,301 patients with DM of the German-Austrian diabetes registry (DPV) and two exemplary patient reports, characteristics of patients with DM and FRDA are compared with classical type 1 or type 2 diabetes.

Diabetes phenotype in FRDA is intermediate between type 1 and type 2 diabetes with ketoacidosis being frequent at presentation and blood glucose levels similar to T1Dm but higher than in T2Dm (356 ± 165 and 384 ± 203 mg/dl).

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Ketoacidosis
Insulin
Oral antidiabetics
Weight

63.2% of FRDA patients received insulin monotherapy, 21% insulin plus oral antidiabetics and 15.8% lifestyle change only, applying similar doses of insulin in all three groups.

FRDA patients did not show overweight and HbA1c levels were even lower than in T1Dm or T2Dm patients, respectively, indicating good overall diabetes control.

FRDADm can be controlled by individualized treatment regimen with insulin or oral antidiabetics. Patients with DM in FRDA may show a relevant risk to ketoacidotic complications, which should be avoided.

1. Introduction

Friedreich ataxia (FRDA) is a multisystemic disorder characterized by neurological, cardiac, and endocrine complications, including progressive afferent and cerebellar ataxia, dysarthria, impaired vibration sense and proprioception, absent tendon reflexes in lower limbs, pyramidal weakness, scoliosis, foot deformity, cardiomyopathy and diabetes mellitus (DM) [1,2]. It affects approximately 1 in 29.000 Caucasians [1–3] and is caused by mutations in the frataxin gene (*FXN*) which leads to a reduction of the mitochondrial protein frataxin and to increased vulnerability of cells to reactive oxygen species (ROS) [4,5]. Whereas about 96% of patients are homozygous for a pathological GAA trinucleotide repeat expansion in intron one of *FXN*, the remaining 4% are compound heterozygous for an intron 1 GAA repeat expansion in one and a point mutation or deletion in the other allele [1,6,7].

Recently Cnop et al. reported that 49% of 41 FRDA patients with no previously diagnosed diabetes had impaired fasting glucose and/ or impaired glucose tolerance [4]. Moreover, 8 to 32% of patients with FRDA are considered to suffer from DM [8–17]. This large variance of DM prevalence may be based on different diagnostic tests and change of diagnostic criteria over time (fasting glucose, HbA1c, oral glucose tolerance testing).

Pancreatic beta cell dysfunction, beta cell loss, insulin resistance and increased body fat mass – the latter was considered to be frequent even among lean patients with FRDA – may contribute to abnormal glucose tolerance and DM. Only some patients show serologic evidence for autoimmunity [18].

According to pre-clinical data, beta cell demise in frataxin deficiency may be the consequence of oxidative stress-mediated activation of the intrinsic pathway of apoptosis although the mechanisms are not well understood [18]. Interestingly, cAMP induction was found to normalize the mitochondrial oxidative status and to prevent activation of the intrinsic pathway of apoptosis in frataxin-deficient beta cells and neurons. Analogues of the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent inhibitory peptide (GIP) may also be protective for frataxin-deficient beta cells. The adenylyl cyclase stimulator forskolin reproduces this effect [4]. Therefore, cAMP induction by incretin analogs may have therapeutic potential to prevent beta cell and neuronal cell loss in FRDA [4,19].

In the YG8R mouse-model of FRDA, different pathogenic mechanisms were confirmed including destruction of pancreatic sensory nerves and pancreatic senescence [20]. Only few studies have focused on this topic suggesting that patients have increased abdominal fat and are insulin resistant. This was not compensated for by increased insulin secretion, resulting in a markedly reduced disposition index, indicative of pancreatic beta cell failure. Loss of glucose tolerance was driven by beta cell dysfunction, which correlated with abdominal fatness. In postmortem pancreas sections, pancreatic islets of FRDA patients had a lower beta cell content [4].

It is still a matter of discussion whether the size of GAA expansion affects the prevalence and severity of DM [14,15,21–24]. In a recent study with 158 patients in a FRDA cohort, age and GAA repeat length predicted fasting glucose and HbA1c levels while insulin and homeostatic model assessment of insulin resistance (HOMA-IR) were not predicted by these parameters. Within the cohort, average BMI was consistently lower than the national average age and was marginally associated with insulin levels and HOMA-IR. Within juvenile subjects, insulin and HOMA-IR were related to age [25].

In contrast to cardiomyopathy, DM is not a typical presenting symptom of FRDA, as hyperglycemia commonly develops approximately 15 years after manifestation of neurological symptoms [11,13,18]. DM onset has often been reported to be acute or even fulminant with ketoacidosis, raising the issue of screening or appropriate diagnostic tools to prevent fulminant onset [8,26,27].

Optimal treatment needs knowledge about the peculiarities of DM among patients with FRDA. In contrast to type 1 and type 2 diabetes, DM in FRDA is rare because of the rarity of FRDA. We were interested in similarities and differences between these diabetes forms and therefore compared observations in a case series of 19 patients with Friedreich Ataxia and diabetes with a large number of patients with type 1 or type 2 diabetes.

2. Methods and patients

2.1. *The 'Diabetes-Patienten-Verlaufsdokumentation'*

DPV database is an electronic computerized program for documentation of patients with all forms of diabetes developed at the University of Ulm [28]. The database includes data of pediatric and adult patients with diabetes from 437 centres in Germany, Austria and Luxembourg. Twice yearly anonymized data are transmitted for centralized analysis at the Institute of Epidemiology and Medical Biometry, University