Latent Autoimmune Diabetes in Adults Associated with Von Recklinghausen's Disease (Neurofibromatosis Type 1)

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Abstract: *Introduction*: Endocrine disorders during Von Recklinghausen's Disease or neurofibromatosis type 1 (NF1) are rare and particularly observed in children. However, autoimmune diabetes mellitus (DM) remains exceptional and unusual during this phacomatosis. We report an original case of Latent Autoimmune Diabetes in Adults (LADA) associated with NF1.

Case Report: A 32-year-old Tunisian male, known to have NF1 since childhood, was admitted for significant recent weight loss (10 kg in one month) with high blood glucose levels. The biological tests confirmed the diagnosis of DM with marked ketoacidosis: fast blood glucose at 16 mmol/l, postprandial glucose at 21 mmol/l, and HbA1c at 9.9%. Radiological and endoscopic investigations did not indicate pancreatic and/or duodenal tumors. Anti-GAD and anti-IA2 autoantibodies were positively confirming the diagnosis of LADA. The assessment of degenerative complications and screening for possible other autoimmune diseases were negative. The evolution was favorable under intensive insulinotherapy.

Conclusion: The association of DM type 1 with NF1 remains exceptional and only four cases are found in the literature, all pediatrics. Our observation is, to our knowledge, the first reporting this association in adult (LADA with NF1).

Keywords: Latent Autoimmune Diabetes in Adults, LADA, neurofibromatosis type 1, Von Recklinghausen's Disease, diabetes mellitus.

INTRODUCTION

First described in 1882 by Von Recklinghausen, neurofibromatosis type 1 (NF1), also known as Von Recklinghausen's disease, is a rare phacomatosis: prevalence estimated at 1/3500 to 1/3000 live births, with autosomal dominant inheritance [1,2].

The mutation responsible for the disease affects the neurofibromatosis gene located on chromosome 17 (17q11.2.) encoding neurofibromin, which physiologically regulates the proliferation and maturation of glial and neuronal cells [1-3].

The clinic is dominated by cutaneous signs (café au lait spots and freckling) and neurological signs (peripheral neurofibromas and gliomas). There are several other rarer manifestations (ocular, cardiac, vascular, bone, endocrine, etc.) marking the systemic nature of this disease and making it serious [1-3].

Diabetes mellitus (DM), however, remains an exceptional and unusual manifestation during this neurofibromatosis [4-6].

We are reporting an original observation of Latent Autoimmune Diabetes in Adults (LADA) associated with NF1.

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CASE REPORT

A 32-year-old Tunisian male, known to have NF1 since childhood, was admitted for significant recent weight loss (10kg in one month) with high blood glucose levels in the emergency department.

The diagnosis of NF1 was held in the presence of several café au lait spots (pigmented birthmarks), of different sizes and diffuse throughout the body (abdomen, thorax, face, and limbs) (Figures **1**, **2**, and **3**), freckling in the axillary and inguinal regions, bilateral Iris Lisch nodules, and multiple subcutaneous neurofibromas in the anterior chest wall, abdomen, back and four limbs (Figures **1**, **2**, and **3**). During childhood, the investigations did not notice any central neurological, cardiac, bony, or intra-abdominal visceral involvement.

The patient was afebrile; his haemodynamic state was preserved and had no cutaneous-mucous jaundice. He reported no diarrhea or abdominal pain.

The biological tests confirmed the diagnosis of DM with marked ketoacidosis: FBG at 16 mmol/l, postprandial glucose at 21mmol/l and HbA1c at 9.9%. The other basic biological examinations were without abnormalities, in particular, the ionogram, creatinine, inflammatory, infectious, and liver tests.

The patient was rapidly and intensively rehydrated with rapid continuous human insulin therapy until the

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disappearance of ketone bodies and normalizations of blood glucose levels.

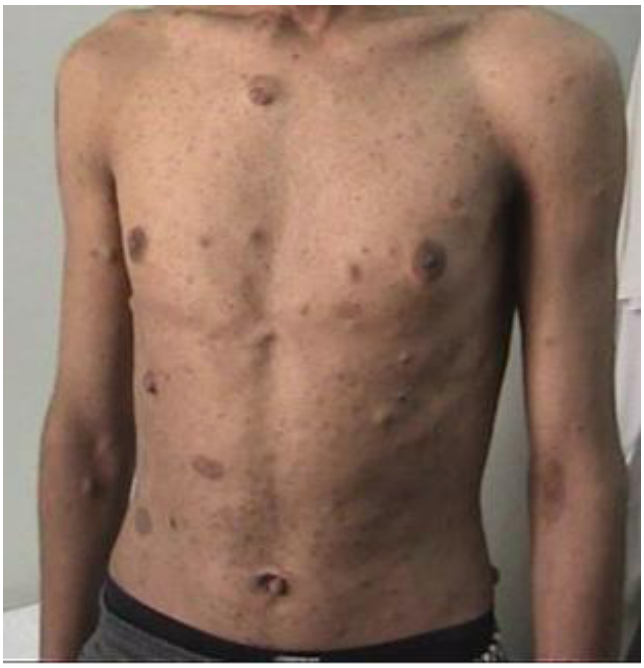

Figure 1: multiple café au lait spots and subcutaneous neurofibromas in the anterior chest wall and abdomen.

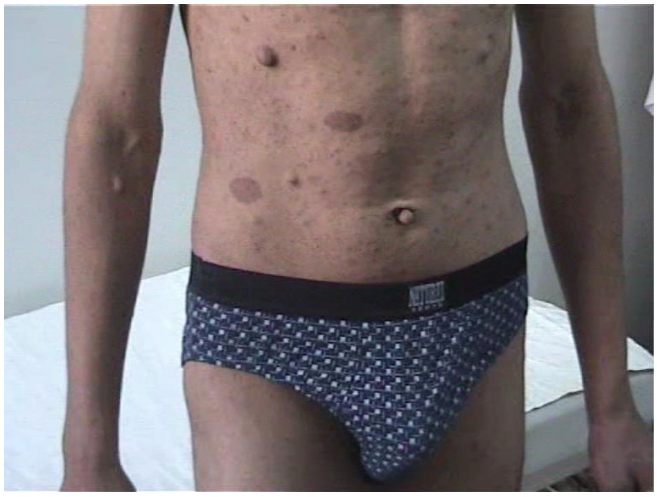

Figure 2: multiple café au lait spots and subcutaneous neurofibromas in the lower abdomen and the anterior faces of the arms.

Radiological and endoscopic investigations did not indicate pancreatic and/or duodenal tumors (abdominal ultrasound, abdominal MRI, and gastroduodenal fibroscopy).

In front of inaugural ketoacidosis, young age, and recent weight loss, the immunological nature of diabetes was suspected and confirmed by the positivity of anti-GAD (253 IU/ml, N<10 IU/ml) and anti-IA2 autoantibodies (22 IU/ml, N<8 IU/ml). Thus the diagnosis of Latent Autoimmune Diabetes in Adults (LADA) associated with NF1 was retained. The assessment of degenerative complications and screening for possible other autoimmune diseases were negative.

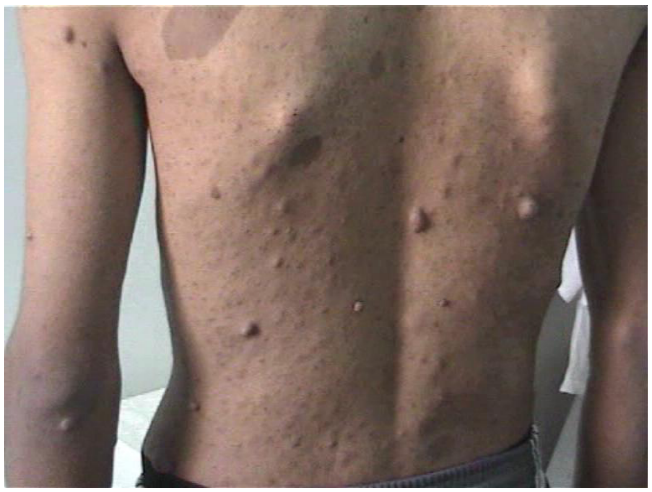

Figure 3: multiple café au lait spots and subcutaneous neurofibromas in the back.

The patient was subsequently switched to fast-acting and long-acting insulin analogues according to complete basal-bolus protocol with favorable evolution.

DISCUSSION

Endocrine disorders during NF1 are rare and are particularly observed in children. They may be of type: central precocious puberty, GH deficiency or on the contrary a GH hypersecretion, obesity with insulin resistance/glucose intolerance, ACTH deficiency, thyrotropin deficiency, and hypogonadotropic hypogonadism [1,7]. These manifestations are most often secondary to the presence of optic pathway gliomas invading or compressing the hypothalamus and sellar region [1,7].

These different endocrine disorders seem, however, to be very underestimated; in fact, in the series of Sani I and Albanese A, these disorders appeared in 55.6% of patients with NF1 during the course of the disease within an average of 2.4 years [7].

Among all endocrine disorders, DM remains exceptional and unusual during NF1 [4-6], and it is classic to say that the risk of diabetes during NF1 is low due to a state of insulin sensitivity significantly increased in subjects with this disease compared to the general population, even after adjusting for age, sex, and BMI [8].

These findings were validated by several comparative studies and using several indices of insulin resistance and insulin sensitivity: FBG, postprandial glucose, HbA1c, HOMA-AD, HOMA-IR, ALR, liptin, visfatin,... [8], and in major national studies of morbidity and mortality [9-11]: Martins AS, showed that the risk of having a high FBG (defining diabetes mellitus) is 89% lower among subjects with NF1 compared to the general population matched for age, sex, and BMI [12], and in the series of 8,579 subjects with NF1, Madubata C, noted a prevalence of DM of only 2.4% compared to a general prevalence in the population of 3.7%, (odds ratio of 0.4) [9].

The first description of the association of DM with NF1 dates back to 1941 by Halperan SR *et al.* [13] and since then only sporadic cases of DM have been reported in this disease. It is type 2 diabetes [10,11], type 1 diabetes [4,6,14,15] and secondary diabetes due to a somatostatinoma-type neuroendocrine tumor [5,16,17]. The exact frequency of glycemic abnormalities during NF1, however, seems to be very underestimated; they were noted in 11.1% of pediatric forms of the disease during prolonged follow-up [7].

The exact mechanism of DM during NF1 remains unclear and several hypotheses are discussed. Hyperglycemic states during NF1 may be secondary to hypersomatostatinemia, exerting an inhibitory effect on insulin secretion [5,17]. This hypersomatostatinemia is most often related to a pancreatic or duodenal somatostatinoma-type neuroendocrine tumor, which in the context of NF1 is part of "syndrome of multiple endocrine neoplasia" type III [5,18]. In these cases, glycemic abnormalities normalize after surgical excision of the tumor [17].

A second hypothesis less evoked is the protective role of mutated neurofibromin? Indeed, studies on the animal model have shown that physiological neurofibromin plays a role in regulating the functions of the hypothalamus and pituitary gland, which are involved in the global energy balance of the body [12,19].

Exceptionally, an immunological disorder may explain cases of type 1 DM, as well as the sporadic association of NF1 with other autoimmune diseases [4,6,15]. The review of the literature found only four cases of type 1 diabetes associated with NF1 [4,6,14,15]. To the best of our knowledge, our observation is, the fifth case reporting with this association. It is characterized in addition by the late onset of diabetes in adulthood; the other observations already reported were all pediatric.

CONCLUSION

As rare as it may be, the association of DM with NF1 must be known by the clinician, given the particular prognostic and therapeutic implications, especially since diabetes may be the first manifestation of the disease. The causes of diabetes can be mainly a pancreatic or duodenal somatostatinoma that must be diagnosed and treated in time, more rarely a type 2 diabetes in relation to endocrine abnormalities specific to NF1 (obesity/insulin resistance/glucose intolerance), and exceptionally type 1 autoimmune diabetes. Our observation is, to our knowledge, the fifth reporting the association of type 1 DM to NF1 and the first of LADA type DM. This association again raises the immunological disturbance suspected of NF1.

ABBREVIATIONS

ACTH = Adrenocorticotropic hormone

Anti-GAD = Anti-glutamic acid decarboxylase antibodies

Anti-IA2 = Anti-tyrosine phosphatase-related islet antigen 2 antibodies

ALR = Adiponectin/leptin ratio

BMI = Body mass index

FBG = Fasting blood glucose

GH = Growth hormone

HbA1C = Glycated hemoglobin A1c

HOMA-AD = Homeostasis model assessment adiponectin

HOMA-IR = Homeostasis model assessment insulin resistance

MRI = Magnetic resonance imaging

CONFLICTS OF INTEREST

No conflicts.

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