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Clinical, immunological, and genetic investigations in a rare association of type 1 diabetes with xeroderma pigmentosum

Ocena kliniczna, immunologiczna i genetyczna w rzadkim współwystępowaniu cukrzycy typu 1 z *xeroderma pigmentosum*

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Abstract
Xeroderma pigmentosum (XP) is a rare genodermatosis predisposing to skin cancers. Autoimmune diseases related to XP are rarely discussed in the literature. Type 1 diabetes (T1D) has been associated with other genodermatoses like Cockayne syndrome, but it has never been described in XP. In the present study, we report the rare occurrence of T1D in XP patients. Five XP patients belonging to 4 consanguineous families originating from different regions of Tunisia were investigated. Their ages ranged between 8 and 18 years. All the patients had a severe hypovitaminosis D. All the patients had positive GAD antibody levels, and 4 of them had familial history of other autoimmune diseases. The spectrum of XP was variable in all the patients, with dermatological and neurological symptoms, and the occurrence of some cancers. Various hypotheses have been proposed to explain this association, among of which we cite the role of immunomodulation and down-regulation of ATP-dependent DNA excision repair protein genes, implying that impaired DNA repair may contribute to the development of some autoimmune diseases. Vitamin D_3 deficiency secondary to sun protective measures was found in all patients and thus may play a role in increasing T1D risk in these patients.
Key words:
xeroderma pigmentosum, type 1 diabetes, autoimmunity, DNA, vitamin D_3.

Introduction

Xeroderma pigmentosum (XP) is a rare autosomal recessive genodermatosis predisposing to skin cancers. It is characterized by skin hyperpigmentation, premature photo-ageing, and early onset of skin cancers [1]. While XP remains a rare condition in Europe at about one per million inhabitants, its incidence in Tunisia is about one per 10,000 inhabitants, given that consanguineous marriages are very common [2]. Xeroderma pigmentosum is due to a defect in the nucleotide excision pathway [3]. There are several genetically related disorders caused by this type of mutation [4]. Patients affected by these diseases are phenotypically different despite sharing some of the same mutated genes as XP patients. These conditions include, among others, Cockayne syndrome and cerebro-oculo-facio-skeletal syndrome [5].

In addition to dermatological manifestations, XP patients may present with endocrinological manifestations, most commonly thyroid nodules and rarely diabetes. Several studies on North African XP patients have found multiple thyroid nodules, diabetes, and thyroid adenocarcinomas in young patients with inherited mutations essentially in the XPC gene [6].

On the other hand, data on autoimmune diseases related to XP are sparse in the literature [7]. Type 1 diabetes (T1D) has been associated with other genodermatosis like Cockayne Syndrome but has never been previously described in XP [8]. Patients with XP have a marked DNA-repair deficiency and immunomodulation that may increase the risk of developing autoimmune diseases [1]. Some other hypotheses are discussed, among which we cite the putative role of vitamin D_3 deficiency caused essentially by sun protective measures in these patients, which is widely considered as a major cause of increasing the risk of developing T1D.

In this study, we report the occurrence of T1D in 5 XP patients, through which we discuss the physiopathological hypotheses suggesting a possible association between these 2 disorders.

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Material and methods

Patients

Five XP patients belonging to 4 consanguineous families originating from different regions of Tunisia were investigated. Their ages ranged between 8 and 18 years. These patients were first diagnosed with T1D in the Endocrinological Department. The study was evaluated and approved by the institutional Ethics Committee and conducted according to the principles of the Declaration of Helsinki.

Methods and explorations

Written informed consent was obtained from the parents of minor children or their legal guardians. We collected information about family history, consanguinity, affected members, and associated diseases through a structured questionnaire.

Deoxyribonucleic acid (DNA) was extracted from all the patients using peripheral venous blood samples according to standard salting-out protocols [9].

Molecular genetic testing was performed by sequencing the sixth exon of the *XPA* gene and the ninth exon of the *XPC* gene to screen for the recurrent mutation in the North African population.

We analysed the concentration of glutamic acid decarboxylase (GAD) and insulinoma antigen 2 (IA2) antibodies in patients suspected of T1D. The diagnosis of T1D was established based on the positivity of at least one of these antibodies.

All of the 5 patients underwent an autoimmune screening consisting of the analysis of anti-thyroperoxidase, anti-transglutaminase, anti-gliadin, and anti-endomysium antibodies, to detect thyroid dysfunction and celiac disease.

The other autoimmune investigations were performed according to the clinical context. Vitamin D_3 was also sampled in all the patients.

Case reports

The patients' clinical, immunological, and genealogical characteristics are summarized in Table I. All the patients had severe hypovitaminosis D (normal range > 30 ng/ml).

Patient 1

This patient was a 17-year-old Tunisian man, the fifth child of the family. Pregnancy and delivery went well. At birth, he was hypotrophic and weighed 1900 g. The patient had a family history of T1D but no other personal autoimmune diseases.

He was diagnosed with T1D at the age of 8 years (antibodies anti GAD +) revealed by a severe diabetic ketoacidosis concomitant with the onset of XP symptoms. After that, a progressive intellectual and cognitive decline and a break in the growth curve have been observed. He had a normal development until the age of 15 years. He developed a progressive perception deafness. The neurological examination revealed an important spasticity and a cerebellar ataxia. Skin examination found xerosis and poikiloderma. He had a beaked nose, and large protruding ears. Mutational analysis confirmed the diagnosis of XPA with a nucleotide variation c.682C>T (exon 6) leading to proteic variation of p.Arg228.

Patients 2 and 3

Two older brothers, with a sibling of 3 boys, were diagnosed with XP discovered at the age of 3 years. They were respectively 12 and 13 years old. They both had a peripheral neuropathy with decreased superficial and deep sensitivity. Despite good photoprotection, they had several scars of tumour excoriations on the face and members. They had multiple retinal tumours, and the younger of the 2 brothers had already developed bilateral blindness.

They were diagnosed with T1D at the ages of 6 and 9, respectively. They had a family history of autoimmune diseases or XP. The older brother developed cardinal symptoms with weight loss, polyuria, and polydipsia. His glycated haemoglobin (HbA_{1c}) at diagnosis was 9%. Whereas the younger one was discovered at an earlier stage of the disease with minor symptoms and a lower HbA_{1c} at 8.6%. No other autoimmune diseases were found.

They were both diagnosed with XPC with a nucleotide variation c.1643_1644del (exon 9) leading to proteic variation of p.Val548Alafs*25.

Both patients responded well to insulin therapy. However, therapy education for the blind brother was complicated because he depended on his family members to ensure his injections as well as insulin titration.

Patient 4

This patient was an 11-year-old boy, the fourth of 5 children, born from a second-degree consanguineous marriage with no familial history especially for XP. He was diagnosed with XP at the age of 10 years, complicated by a nasal basal cell carcinoma and a thyroid nodule discovered recently (classified Eu-TiRads 4) with a benign cytopuncture. Mutational analysis confirmed the diagnosis of XPC with nucleotide variation c.1643_1644del (exon 9) leading to proteic variation of p.Val548Alafs*25. Despite photoprotection, he developed several sunburn reactions. This patient had also a peripheral neuropathy with decreased superficial and deep sensitivity.

Diabetes was revealed at the age of 10 years, with polyuria and polydipsia evolving for 3 months. Hashimoto hypothyroidism was diagnosed following the T1D diagnosis, through a systematic screening for other autoimmune diseases, with TSH = 5.6 mIU/ml (NR = 0.5–4.5 mIU/ml) and FT4 = 6 pg/ml (NR = 7–19 pg/ml), and he was substituted with adequate hormonal treatment.

Patient 5

This patient was a 12-year-old girl. She was the first child of healthy second-degree consanguineous Tunisian parents with no familial history for XP. Even though the diagnosis of XP at the age of 3 years allowed her to have an early photoprotection, she still developed sunburn reactions along with several basal cell carcinomas in the left eye. Neurological disorders and psychomotor development delay were not observed in this

Table I. Clinical, immunological, and genetic characteristics of the patients

Patient	Sex	Type of XP	Genotype results	Age at diagnosis of T1D	Familial history of autoimmunity	Personal history of autoimmunity	Auto-antibodies	HbA_{1c} (%)	Vitamin D (ng/l)
1	Male	XPA : nucleotide variation c.682C>T (exon 6) leading to proteic variation of p.Arg228	NM_000380.3(XPA):c.[682C>T(;)682C>T]	8	T1D	_	Anti-GAD + Anti-IA2 –	10.6%	< 4
2	Male	XPC : nucleotide variation c.1643_1644del (exon 9) leading to proteic variation of p.Val548Alafs*25	NM_004628.4(XPC):c.[1643_1644del(;)1643_1644del]	6	T1D	_	Anti-GAD + Anti-IA2 –	9%	6
3	Male	XPC : nucleotide variation c.1643_1644del (exon 9) leading to proteic variation of p.Val548Alafs*25	NM_004628.4(XPC):c.[1643_1644del(;)1643_1644del]	9	T1D	_	Anti-GAD + Anti-IA2 –	8.6%	9
4	Male	XPC : nucleotide variation c.1643_1644del (exon 9) leading to proteic variation of p.Val548Alafs*25	NM_004628.4(XPC):c.[1643_1644del(;)1643_1644del]	10	_	Hashimoto hypothyroidism	Anti-GAD + Anti-IA2 –	15%	< 4
5	Female	XPA : nucleotide variation c.682C>T (exon 6) leading to proteic variation of p.Arg228	NM_000380.3(XPA):c.[682C>T(;)682C>T]	10	Hashimoto hypothyroidism	_	Anti-GAD + Anti-IA2 –	11%	< 4

XP – xeroderma pigmentosum; T1D – type 1 diabetes; HbA_{1c} – glycated haemoglobin; anti GAD and IA2 – auto antibodies anti GAD and anti IA2.

patient. Recently, she had been diagnosed with leukaemia and was treated by chemotherapy.

At the age of 10 years, she was diagnosed with T1D revealed by keto-acidosis without triggering factors. Auto antibodies check-up showed a positivity for anti-GAD antibodies without other personal autoimmune diseases. However, a family history of Hashimoto's disease was found. Mutational analysis confirmed the diagnosis of XPA with nucleotide variation c.682C>T (exon 6) leading to proteic variation of p.Arg228.

Discussion

Xeroderma pigmentosum is a rare clinical disorder associated with photosensitivity and a high risk of cutaneous malignancy in sun-exposed areas [10]. Defects in any of 7 proteins, designated XPA to XPG, can confer an XP phenotype, and these proteins jointly operate in nucleotide excision repair, a mechanism that handles the damage induced by ultraviolet (UV) exposure. Consequently, cells in XP condition are highly sensitive to UV irradiation.

While diabetes mellitus is associated with some genodermatoses such as Cockayne's syndrome, AT and XP are associated with an increased prevalence of diabetes in family members [11]. This suggests a site sensitive to breakage in a diabetes susceptibility gene. The gene coding for an enzyme that alters the three-dimensional organization of DNA excision repair protein (ERCC-3) has been shown to be involved in the human repair disorders in XP and Cockayne's syndrome [12]. Interestingly, 2 related genes (*ERCC-1* and *ERCC-2*) have been mapped to chromosome 19 and are now known to be very close to the gene for myotonic dystrophy [13]. DNA breakage may be implicated in the mechanism of diabetes in Cockayne's syndrome, AT, XP, and myotonic dystrophy. However, we could not find in the literature the exact mechanism by which the patient developed diabetes mellitus. Considering that genodermatoses are discovered in youth, the probability of T1D is higher [14].

Some hypotheses are discussed in the literature regarding the mechanism of autoimmune reaction in XP. Immunomodulation has been reported in some but not all XP patients [15]. Impaired natural killer cell cytotoxicity found in T1D has been described. Defective interferon production has been suggested as a potential mechanism, but it is currently still enigmatic [16]. UV damage is known to modulate the immune response in normal cells, and the presence of elevated unrepaired DNA damage in genodermatosis patients is likely to enhance this immunosuppression [17]. Thus, it appears that at least a part of the immunomodulation in XP develops as a consequence of the repair defect rather than as a direct result of the abnormal XP proteins impairing immune development. In support of this, defective post-UV immunity has been observed in XP-A mice [18].

The process of UV-induced DNA damage repair is also known to require adenosine triphosphate (ATP), and the main function of mitochondria is to generate ATP through oxidative phosphorylation [15]. Accordingly, down-regulation of ATP-dependent DNA excision repair protein ERCC genes and mtDNA-encoded genes implies that impaired DNA repair and ATP synthesis, or increased apoptosis, may contribute to the various manifestations of some autoimmune diseases such as systemic lupus and may also induce T1D [7].

Another hypothesis may arise from treating XP patients with sun protection measures leading naturally to a vitamin D_3 deficiency. The relationship between vitamin D_3 deficiency and T1D mellitus has been established for a long time [19]. Several studies on animals as well as on humans have confirmed that T1D mellitus is associated with vitamin D_3 deficiency as a leading disease or as a consequence [20]. Furthermore, supplementation of vitamin D_3 in young children is proven to reduce the risk of T1D [21]. Vitamin D_3 is produced by the interaction of UV with the skin. However, rigorous sun protection is necessary in XP, beginning as soon as the diagnosis is suspected, to prevent continued DNA damage and disease progression. Individuals with XP should avoid exposing the skin and eyes to UV radiation. This can be ensured by wearing protective clothing such as hats, hoods with UV-blocking face shields, long sleeves, trousers, and gloves. All these measures will lead to a vitamin D_3 deficiency and increase autoimmune risk, as found in several works [22, 23]. Because people with XP avoid UV, oral dietary supplements should be taken as needed to avoid complications of inadequate vitamin D_3 levels and to decrease the risk of concomitant autoimmune diseases.

Conclusions

In this study, we reported the first cases of the association between T1D and XP. Xeroderma pigmentosum remains a rare disorder of autosomal recessive inheritance. It is based on a genetic defect in the DNA repair system. Patients with XP have a marked DNA-repair deficiency and immunomodulation that may increase the risk of developing autoimmune diseases. Another major hypothesis that we discussed is the putative role of vitamin D_3 deficiency caused essentially by sun protective measures in these patients, which is widely considered as a major cause of increasing the risk of developing T1D. This enhances the importance of oral supplementation to keep vitamin D_3 levels within normal ranges.

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