CHAPTER 2

Clinical Features of Xeroderma Pigmentosum

Ulrich R. Hengge* and Steffen Emmert

Background

Xeroderma pigmentosum (XP) was first described in 1874 by Hebra and Kaposi. Albert Neisser was the first to report neurological abnormalities associated with XP in 1883. XP is an autosomal recessive disease with defective nucleotide excision repair (NER). It is characterized by easily recognizable clinical hallmarks (Table 1). These manifestations are due to cellular hypersensitivity to ultraviolet (UV) radiation resulting from a defect in DNA repair. Two types of NER exist: global genome (GG-NER) and transcription coupled (TC-NER). Eight complementation groups, XPA-XPG, corresponding to defects in the corresponding gene products of XPA-XPG genes and XP-variant, have been described. These entities occur with different frequencies (e.g., XPA is relatively common, whereas XPE is fairly rare) and they differ with respect to disease severity (e.g., XPG is severe, whereas XPF is mild) and involvement of skin, central nervous system and ophthalmological manifestations (Table 2). Cockayne syndrome rarely occurs together with XPB, XPD and XPG.

In addition to the DNA repair defects, UV radiation also exerts pronounced immunosuppressive effects that are likely to be involved in the pathogenesis of XP. Although typical symptoms of immune deficiency, such as multiple infections, are not usually observed in patients with XP, prominent depletion of Langerhans cells, induced by UV radiation, has been described in XP patients. Various other defects in cell-mediated immunity such as impaired cutaneous responses to recall antigens, impaired lymphocyte proliferative responses to mitogens and decreased production of interferon as well as reduced natural killer cell activity have been detected in XP patients.

Epidemiology

The frequency of XP in the United States is about 1 case/250,000 inhabitants. Not uncommonly, parental consanguinity and familiarity are present in patients with XP.

XPC is the most common group in the United States, constituting almost 1/3 of XP patients. The unscheduled DNA synthesis is usually between 15-30% of normal. Symptoms for neurological disorders are rare in XP-C. XPD is the second most common type of XP in the United States and accounts for the majority of US patients with symptoms for neurological disorder being present in about half of all those patients, while the cutaneous and immunologic presentations are quite heterogeneous.

Internationally, the incidence of XP is about the same in Europe, whereas it is higher (1:40,000) in Japan, where XPA is the most common group. In Europe XPA and XPC are the two most prevalent forms of XP. There is no gender preference. As an autosomal recessive disorder, there is usually no positive family history as the heterozygous parents are clinically healthy.

* Corresponding Author: Ulrich R. Hengge — Department of Dermatology, Heinrich-Heine-University, Düsseldorf, Germany. Email: ulrich.hengge@uni-duesseldorf.de

Clinical Features of Xeroderma Pigmentosum

Table 1. Clinical hallmarks of xeroderma pigmentosum

- Severe photosensitivity (painful sunburns in early childhood)
- Poikiloderma
- Dryness (xerosis)
- Premature skin aging
- Malignant tumors (squamous cell cancers, basal cell cancers and melanoma), most often on face, head and neck
- Various neurological and ophthalmological symptoms and manifestations

Table 2. Characteristics of xeroderma pigmentosum complementation groups

<table>
<thead>
<tr>
<th>Complementation Group</th>
<th>Frequency (%)</th>
<th>Skin Cancer</th>
<th>Neurological Involvement</th>
<th>Ophthalmological Involvement</th>
<th>Gene Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>XPA</td>
</tr>
<tr>
<td>B</td>
<td>0.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>XPB/ERCC3</td>
</tr>
<tr>
<td>C</td>
<td>27</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>XPC</td>
</tr>
<tr>
<td>D</td>
<td>15</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>XPD/ERCC2</td>
</tr>
<tr>
<td>E</td>
<td>1</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>DDB2/XPE/p48</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>XPF/ERCCC4</td>
</tr>
<tr>
<td>G</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>XPG/ERCC5</td>
</tr>
<tr>
<td>Variant</td>
<td>23.5</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>XPV/hRAD30</td>
</tr>
</tbody>
</table>

Dermatological Manifestations

In general, skin problems precede neurological and ophthalmological symptoms. Several key cutaneous features are usually found. While babies are normal at birth, in the first years of life, diffuse erythema, scaling and pronounced freckle-like pigmentation develop (Fig. 1). In accordance with the increased light sensitivity, changes are seen over light-exposed areas, in particular face, head and neck and in severe cases they subsequently appear in the lower legs and even the trunk. One needs to become alert, when babies present with severe solar dermatitis/sunburn, often associated with constant crying, for which no other explanation can be found. The sunburn will usually persist for extended periods of time, not uncommonly, for several weeks and may include blister formation upon minimal sun exposure.

Once the erythema has resolved, multiple freckles on sun-exposed skin areas cause mottled pigmentation, telangiectasias and actinic damage. XP is one of the few diseases that can cause poikiloderma at an early age (Fig. 2). Poikiloderma is characterized by erythema, hyper- and hypopigmentation as well as scarring and telangiectasias. As the skin suffers actinic damage, the surface becomes atrophic and dry, which has led to the term "xeroderma" (dry skin) for this condition (Fig. 3).

The incidence of tumors is about 1000-fold increased as compared with the normal population. The process of malignant transformation in XP has been estimated to be around 8 years as compared with 60 years for a representative control cohort. The mean patient age of developing skin cancer is 8 years in XP patients and for the onset of actinic damage around 1-2 years of age.

Characteristically, children or adolescents develop large areas with field cancerization including multiple actinic keratoses, in situ squamous cell cancer and malignant skin tumors (Fig. 3). Upon the malignant tumors, the UV light-induced cancers like squamous cell cancer, basal cell cancer and lentigo maligna melanomas are predominating (Fig. 4). Especially for melanoma, the role of UVB is widely accepted. Interestingly, the total UV-dose plays an important role in lentigo malignant