Xeroderma Pigmentosum A
Brian Ginsberg, Amy Shehata, Charles Butler

Xeroderma Pigmentosum (XP) is a disorder in which the DNA repair mechanisms used to fix damage caused by ultraviolet light are inoperative. It occurs in every ethnic group and is distributed between men and women equally. In the United States alone, 1 in 250,000 people have some type of this disease. Specifically, there are at least 7 forms of this disease which manifest themselves in similar ways and are characterized into the subgroups XPA through XPG. For the purpose of this paper, we will be referring to the most common form, Xeroderma Pigmentosum Complementary Group A (XPA).

In the late 1960s, James Cleaver began exploring this disease upon noticing that the skin fibroblasts in individuals with XPA lack the ability to repair ultraviolet radiation damage to DNA by the usual method of excising the damaged portion and inserting new bases into the DNA. His observations became more specific in 1994 when he outlined the precise mechanism of nucleotide excision repair and how it related to XPA. For instance, the first steps in the repair mechanism involve the use of the DNA-binding proteins XPA and XPE. The damaged region is cut by two nucleases, a ERCC1/ERCC4 complex and XPG, which act on both single and double stranded DNA. Following this, the correct DNA sequence is synthesized using DNA polymerase delta/epsilon and ligase. At the same time as Cleaver was discovering this, another team discovered the interrelation of XPA and ERCC1, showing that XPA may be responsible for orienting the initiation complex, which contains the ERCC1, to the damaged site on the DNA. They then used site-specific mutagenesis of XPA in order to show the functional relevance of this relationship, which revealed that this association between XPA and ERCC1 is required in the nucleotide excision repair mechanism and that the role of XPA is for the recruitment of ERCC1. Specifically, XPA, ERCC1 and ERCC4 formed a ternary complex that participates in both the recognition and repair part of the pathway.

The XPA gene is located on chromosome 9q22.3. With respect to the specific mutations of the gene, it was found that most mutations were deletions and splice-site mutations in exon 3, intron 3, or exon 4, all of which lead to frameshifts within the region. A point mutation was also found within intron 3, which led to a new splice acceptor site, competitively inhibiting the binding to the other acceptor site. The more severe cases of the disease had mutations in the DNA-binding regions, as opposed to those found in the C-terminus which interacts with the TFIIH transcription factor.

Once the XPA gene has been mutated, the frequency of mutations in other genes rises dramatically since the repair mechanism has been shattered. Absorption of the high energy UV light leads to the formation of pyrimidine dimmers such as Cyclobutate-Pyrimidine-Dimers (CPDs) and pyrimidine-6-4-pyrimidone (6-4PP) photoproducts. If this mutation affects tumor suppressor genes, such as p53, or protooncogenes, this could result in cancer.

Diagnostic criteria is usually based on visual symptoms and occurs in early infancy, specifically in the first 2 years. Usually, a child will have severe sunburn after their first time being expose to the sun which is often a good clue that they have XPA, although not a definitive diagnostic measure. Conclusive diagnosis can be therefore done by measuring the DNA repair factors in tissue samples from skin or blood. Very recently, chorionic
villus sampling has been done prenatally to test for the disease, although this is only performed if there is history of the illness in the family.

Xeroderma pigmentosum has a series of symptoms. Some of these symptoms are visible and others are less obvious. The disease usually progresses through three stages.\(^9\) It is useful to note that in these three defined stages the skin always appears normal at birth, therefore it is difficult to detect xeroderma pigmentosum in the beginning of the patient’s life. After being born with normal skin coloration, the first signs of the disease appear at or around 6 months after birth. The first stage of xeroderma pigmentosum is when the baby starts displaying a red face and irregular freckles after being exposed to sunlight — specifically: ultraviolet light. This reddening and scaling along with freckles occurs even if the skin is exposed for short periods of time. Often times, irregular dark spots may also begin to appear in this first stage. After a short while, the reddening and dark spots spread to the rest of the neck, and onto the legs. In severe cases, the first stage involves reddening of the trunk. These signs diminish in the wintertime when the child is usually covered and sun exposure is minimized.

After the child has been exposed to the sun multiple times, the disease will progress into the second stage. This stage is more obvious and visible than the first stage which is sometimes mistaken for simple sun-burns. This second stage of xeroderma pigmentosum is defined by poikiloderma. Poikiloderma is characterized by development of irregular patches of lightened and darkened skin. Also present in this second stage is a spider web-like collection of blood spots as well as blood vessels that are seen through the skin. There is also thinning of the skin at the second stage. Variability is notable in this second stage and the severity of these symptoms can be markedly different from one individual to the next. In some cases, the whole body becomes enveloped with these blood spots and thinning skin. In other cases, this second stage is less severe with only minor spots and a little thinning of the skin.

By far the worst and most visible stage is the third stage. Although the second stage is easy to see in most individuals, sometimes second-stage xeroderma pigmentosum patients are not detected; the third stage is impossible to miss. In the third stage, the development of solar keratosis occurs. This includes deep noticeable sun marks in the face and often lesions that are able to bleed. Skin cancer also occurs in this third stage. This usually occurs at about 4-5 years of age and is more prevalent in sun exposed areas such as the face, neck and arms. People who have xeroderma pigmentosum have a much higher chance of having cancer. Common skin cancers, basal cell carcinoma, squamous cell carcinoma, and melanoma occur at much higher rates with people who have this disease.

The following are specific prognostic statistics to help understand the frequency of the consequences of the illness, as determined by examining 132 patients with Xeroderma Pigmentosum. Seventy percent of the patients had malignant skin neoplasms with a median age of occurrence at 8 years, which is 50 years earlier than the average United States population. In addition, 57% presented with basal or squamous cell carcinoma and 22% with melanoma. In general, melanomas and other cancers were increased by 1000 times the rate of the population under 20 years of age.\(^{10}\)

Other than the previously mentioned symptoms in these three stage. There are other symptoms involved as well. Eye problems occur in nearly 80% of xeroderma pigmentosum patients. This is when the eye becomes extremely sensitive to the sun and the patient usually squints a lot. The eyes are easily irritated. They look bloodshed and
clouded. Conjunctivitis may also occur on some patients. Non-cancerous as well as cancerous growths on the eyes may occur. The major and most common sign of eye irritation though is the squinting due to sunlight sensitivity as well as bloodshot eyes.

Another symptom, but more rare, is neurological problems. Neurological problems occur in 20% of xeroderma pigmentosum patients. These neurological problems can be either mild or severe and can include spasticity, poor coordination, deafness in one or both ears, short stature as well as other development delays. These neurological symptoms may develop in late childhood or early adolescence. These symptoms also tend to worsen over time.

There is currently no known cure for xeroderma pigmantosum. Patients with xeroderma pigmantosum should aim to prevent the damaging effects of UV exposure by avoiding UV light altogether. This means taking certain precautionary measures. First, patients should avoid all sun exposure. It is recommened that they wear protective clothing such as long pants and long shirts, shirts with collars and tightly woven fabrics that will not permit any light to travel through. Hats with wide brims and eyewear with UV protection should also be worn. It is crucial that patients use a sunscreen with a minimum SPF of 30 and that it be applied to all exposed areas of skin. Outdoor activities should be avoided and kept to a minimum if at all necessary. The best solution is to restrict outdoor activities to night time.

A second precautionary measure is to have those with xeroderma pigmantosum examined by someone who is taught to recognize the signs of skin cancer exam. Any suspicious growth or spot should be reported to a physician immediately. In addition to home examinations, patients should be examined by a dermatologist at least every 3-6 months. This will ensure that any suspicious growth is biopsied and that all skin cancers are excised. In addition to dermatologic examinations, the patient should be seen by an ophthalmologist. Yearly testing for potential neurological problems should be done until the age of 20.

Some xeroderma pigmantosum patients that suffer from frequent skin cancers may be prescribed a vitamin A derivative, such as isotretinoin, which may prevent the formation of new cancers (keratoses). In addition, solar keratoses may be treated by cryotherapy or 5-fluorouracil cream.

There are many things that must be considered during a therapeutic intervention with families of people with Xeroderma Pigmentosum. It is an autosomal recessive disease which means that if the child has the disease and his parents do not, his parents are both obligate carriers. Thus, if the parents decide to have another child, there is a one in four chance that it will have the disease. Also, other members of the family are at an increase risk of being heterozygous (carriers). In addition, the individual with Xeroderma Pigmentosum is at an increased risk of having a child with the disease if the other parent is a carrier, although the probability of the other parent being a carrier or having the disease is 1 in 1700 according to population statistics. As for the other members of the family who may be heterozygous for the trait, it is unclear whether this would lead to any symptoms for themselves. In some cases, increased freckling has been linked to heterozygosy. Furthermore, one study once found that in families with individuals with Xeroderma Pigmentosum, blood relatives were statistically significantly more likely than their spousal controls to have nonmelanoma skin cancer. Therefore, these individuals should also be advised of the potential necessity for sun avoidance.
Overall, Xeroderma Pigmentosum is a disorder which as a large effect on the lives of those who have it and on their families as well. Due to this high risks involved, major lifestyle changes have to be made in order to avoid risk of exposure to sunlight and thus risk of complications such as cancer. Currently, programs for children with this disease have been set up to help support a more normal experience for growing up. This includes Camp Sundown, which is a camp where the majority of activities occur at night. Therefore, while this disease is incurable and has a large impact on daily life, it is increasingly becoming a more manageable trait to have.

REFERENCES