DNA Damage and DNA Repair Disease: a Brief Primer – Deborah Tamura, MS RN

Every second of every day since we were conceived, the DNA in our cells is damaged and needs to be repaired. Sometimes the damage is caused by 'cellular waste products' generated inside our own cells; sometimes the damage results from things in the environment such as ultraviolet light (UV) from the sun or harmful chemicals, like those in cigarette smoke. When DNA in a cell is damaged, several things can happen: the cell can die, the cell can stop dividing (but still functions somewhat - this is called cell senescence) or the cell can turn into a cancer cell. So it is in the best interests of our cells and our bodies to rapidly repair any damage to the DNA.

There are many ways to damage DNA including: DNA distorting lesions, double strand breaks, single strand breaks, DNA cross links, base mismatches and a-basic sites. For each type of damage, the cell has a repair mechanism (pathway) to fix the broken DNA.

Cockayne syndrome (CS), Trichothiodystrophy (TTD) and Xeroderma pigmentosum (XP) are three conditions that result, when one of the DNA repair pathways is not functioning properly. This pathway is called the nucleotide excision repair pathway (NER) and it repairs DNA distorting lesions caused by UV from the sun and oxidative damage caused by waste products of cellular activity.

Descriptions of the conditions:

<u>Xeroderma Pigmentosum:</u>

Xeroderma pigmentosum (XP) is a rare inherited disorder. People with this condition cannot repair ultraviolet (UV) damage in the skin, eyes and other UV exposed areas of the body. The most common source of UV is sunlight. The damage caused by UV often leads to the development of many cancers in any sun (UV) exposed area of the body. People with XP have a 10,000 fold increased risk for skin cancer. The cancers often develop in the first decade of life (early childhood). About half of people with XP are very sensitive to UV and will develop severe blistering sun burns after short amounts of sun exposure. These burns can be so severe that child abuse or neglect is suspected. The other half of XP patients do not get sunburns but often develop freckles on sun exposed areas of the body – often by 2 years of age. It is not normal to have freckles this early in life. Following repeated sun exposure the person's skin may be very dry and can look like the skin of someone much older. The eyes of people with XP are particularly sensitive to sunlight and they may be very uncomfortable being around any bright light especially sunlight. UV damages the eyes of XP patients causing 'dry eye' and growths on the surface of the eye called pterygia and pinguecula; the UV damage leads to corneal scarring which can result in blindness. People with XP can also develop cancer on the eyelids and the surface of the eye. Cancers can also occur on the lips and tip of the tongue.

Approximately 20% of people with XP develop progressive neurological problems. Initially, they may begin to lose their hearing and reflexes. Eventually they may have difficulty walking, talking, eating and taking basic care of themselves; in time they may need hearing aids, feeding tube placement, wheel chairs and a full time caregiver. These neurological problems may begin in early childhood or may not start to develop until the second decade of life. MRIs and CT scans show progressive enlargement of the ventricles (normal openings inside the brain) and loss of brain matter.

Mutations in eight different genes in the NER DNA repair pathway (XPA, XPB, XPC, XPD, XPE, XPF, XPG, and XPV) have been found to cause the symptoms of XP. However, research suggests there may be more, as yet unidentified genes causing XP. There is no cure for XP, but early diagnosis, careful UV protection with sunscreens, clothing and avoidance of the sun, can decrease the effects of the condition on the skin and eyes.

<u>Trichothiodystrophy:</u>

Trichothiodystrophy (TTD) is a rare, inherited disease, in which patients have short brittle, sulfur-deficient hair. When the hair from TTD patients is observed under a special polarizing microscope, it shows a distinctive pattern of striping, called "tiger tail banding." TTD patients have a wide variety of other features, including very dry skin, frequent infections, developmental and growth problems. It seems that almost every child with TTD is different and one child may have many complications and another may have only a few problems.

Symptoms of TTD include: photosensitivity, dry, scaly skin (ichthyosis), short brittle hair, intellectual impairment (developmental delay), short stature with poor weight gain, immune problems and eye problems. Most children with TTD have some combination of these health issues. Many children with TTD are very sun sensitive and get sun burns after very short exposures to sunlight. However, unlike XP, patients with TTD do not develop freckling and skin cancer. They often have dry scaly skin and thick nails that tend to peel. Most children with TTD are short and can be very thin, although they eat well balanced meals with lots of calories. They also may be hospitalized frequently for infections. The MRI and CT findings in TTD children include hypo or dysmyelination (abnormal myelin formation). Myelin is the "insulation" that wraps around a nerve fiber. The myelin helps nerve impulses to be transmitted properly. Most children with TTD do not lose brain matter.

Often TTD children will need to have a feeding tube placed to help them gain weight. In addition the majority of children with TTD have some sort of developmental delays; some need special education classes in public schools and others need very extensive care and monitoring of their developmental progress including physical therapy, occupational therapy, speech therapy and nutritional guidance. The majority of children with TTD have vision problems and may need glasses or surgery for cataracts; some also have hearing problems related to repeated ear infections. Serious problems with infectious illness, including, influenza, ear infections, pneumonia and gastroenteritis with dehydration are common in children with TTD. This reflects problems with the immune system. Despite many illnesses and health challenges, children with TTD are generally happy and outgoing.

TTD is also caused by mutations in one of several NER DNA repair genes including XPB, XPD or TTDA. A few children with have mutations in TTDN1, a gene of unknown function not in the NER DNA Repair pathway. Although XPB and XPD mutations are also seen in patients with XP, TTD patients have not been reported to have an increase in cancer.

<u>Cockayne Syndrome</u>:

Cockayne syndrome (CS) is a rare inherited condition that can present in several different ways. CS type I, is the "classic" or most commonly seen form. Many children with CS are very sun sensitive and will sun burn easily. Sometimes, severe sunburn is the first sign that something is wrong. However, unlike XP, most patients with CS do not develop freckling and skin cancer. In CS type I, the children seem normal at birth; however in the first 1 to 2 years of life the child does not grow as fast and begins to show developmental delays. Children with CS type I eventually are much smaller than other children their same age. They can develop cataracts and hearing loss in the first several years of life. They become spastic and have difficulty moving their joints (contractures). The developmental problems are progressive and children with CS type I lose many abilities and need to be in wheel chairs and fed with a feeding tube. Due to this progressive loss of abilities, these children become quite frail and develop problems with their kidneys and livers. CS type II, is a much more severe form of CS and children have many of the CS symptoms at birth. It is also called cerebro-oculo-facial syndrome (COFS) or Pena-Shokeir syndrome type II. The children have little or no development during their life. They often have eye problems such as cataracts at birth. Children with CS type II often develop contractures in the first year of life; this is seen especially in the spine (kyphosis, scoliosis) and joints of the arms and legs. CS type III, is a milder form with symptoms beginning later in childhood with close to normal growth and cognitive development for many years. Brain MRI scans show decreased or absent myelin and cerebral (brain)

atrophy may also be present. CT scans may reveal calcifications of the basal ganglia and other areas in the brain. There is also a form of CS with symptoms of XP or the xeroderma pigmentosum-Cockayne syndrome complex (XP/CS). The children with the XP/CS type of CS will have short stature and the same skin symptoms as children with xeroderma pigmentosum, including early skin freckling and in some cases, skin cancers. However, a child with the XP/CS complex may not the severe skeletal problems or contractures seen in the other forms of CS. All children with CS have typical facial features including deep set eyes, large ears and a thin 'aged appearance' to the face. Cockayne syndrome is caused by mutations in one of several genes involved in the NER DNA repair pathway: CSA, CSB, XP-D, XP-B, XP-G and XP-F

Treatment

There is currently no cure for XP, TTD and CS so UV protection, treatment of cancers, educational programs, assistive devices, physical therapy and feeding tube placement when needed are important in caring for children and adults with NER DNA repair diseases. Every child and adult with these conditions is different so health care needs to be tailored to each child/adult's individual needs. For example, hearing loss can be treated with hearing aids; cataracts and other eye problems can require surgery. Use of sunscreens and sunglasses and avoidance of excessive sun exposure are helpful, especially when a child is particularly sun sensitive. Since these children and adults can have many health problems they need to be followed closely by their doctors. Current research in XP, TTD and CS is investigating why children and adults have such severe health problems and how mutations in the NER DNA repair genes affect different cellular functions. Research is also continuing into how to best treat the symptoms of these conditions.

Comparison of Clinical and Laboratory Abnormalities in
Xeroderma Pigmentosum
Cockayne Syndrome and Trichothiodystrophy

	XP	CS	TTD
Sun sensitivity	**+**	**+**	**+/-**
Skin pigmentation /cancer	**++**	**+/-**	**-**
Eye problems	**+**	**+**	**+**
Neurological problems	**+/-**	**++**	**++**
NER DNA repair defect	**+**	**+**	**+**
Environmental influence on disease	**++**	**-**	**-**
Developmental problems	**+/-**	**++**	**++**

Further information:
I have included several papers from medical journals for additional reading.