Neurology of XP

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Outline

• General medical precautions
• Neurological complications of XP
• Our biorepository
• Natural history study
General medical precautions
Metronidazole is contraindicated

Metronidazole-Induced Hepatitis in a Teenager With Xeroderma Pigmentosum and Trichothiodystrophy Overlap

- ERCC2-related XP-TTD
- Adolescent female
- Hepatitis was reversible

Metronidazole-induced hepatotoxicity in a patient with xeroderma pigmentosum
A case report

- XP, genetic subtype not reported
- 44-year-old man
- Liver function recovered but patient died from pneumonia soon afterwards
Metronidazole is now contraindicated in CS

Risk of Hepatotoxicity and Death in Patients with Cockayne Syndrome

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Obtain liver function tests prior to the start of therapy, within the first 2-3 days after initiation of therapy, frequently during therapy and after end of treatment. Discontinue metronidazole if elevation of liver function tests occurs, and monitor liver function tests until the baseline values are reached.

Advise patients with Cockayne syndrome to stop taking metronidazole immediately if they experience any symptoms of potential liver injury, such as abdominal pain, nausea, change in stool color or jaundice, and to contact their healthcare provider.

The risk appears to be similar in XP, should metronidazole be contraindicated in XP as well?
Fluid management

• Patients with DNA repair disorders appear to be vulnerable to fluid overload, particularly when receiving intravenous fluids
• Fluid overload can lead to edema and fluid accumulation, including in the lungs
• Fluid doses should be calculated based on the patient’s actual weight, not the expected weight for age
• Avoid or minimize intravenous fluid boluses
• Whenever feasible and safe, administer less than the usual calculated “maintenance intravenous fluids”
Neurological complications of XP
Frequency of neurological complications

• Various estimates indicate that a small but distinct minority of XP patients have neurological complications
  • 18% (152 of 830, Kraemer et al, Arch Derm 1987;123:241-250)
Specific neurological complications (Kraemer)

• Among 152 individuals known to have XP with neurological issues:
  • Intellectual disability  80%
  • Motor problems       30%
  • Microcephaly          24%
  • Areflexia             20%
  • Neurological deterioration  18%
  • Hearing problems      18%
  • Speech problems       13%
  • Abnormal EEG          11%
XP genes associated with neurological issues

- **ERCC2** (*XPD*)
- **ERCC3** (*XPB*)
- **ERCC4** (*XPF*)
- **ERCC5** (*XPG*)
- **XPA**

- Fassihi et al, *Proc Natl Acad Sci USA* 2016;113:e1236-124
- This list is not meant to be exclusive, and will likely expand in the years to come
Neurodevelopmental disorders

• Language, fine motor, gross motor, and social delays
• These may be present in various combinations depending on the individuals
• Hearing problems will worsen these issues
• Diagnosis: developmental and neuropsychological testing
• Therapy: combination of physical, occupational, and speech therapies, hearing aids for hearing loss
Neuropathy

- Clinical features
  - Areflexia or hyporeflexia
  - Distal paresthesias and numbness
  - Distal weakness
- Tends to be axonal rather than demyelinating
- Can be sensorimotor or sensory
- Diagnosis: EMG
- Therapy: physical therapy, occupational therapy, sometimes gabapentin for neuropathic pain
Median sensory study (left)

Sural sensory study (right)

Tremors

• Many though not all tremors are caused by dysfunction in a part of the brain called the basal ganglia
• Some tremors arise from another part of the brain called the cerebellum, especially if they are triggered mostly by movement
• Severity of tremors range from mild to severe and disabling
• Diagnosis: history and physical examination, sometimes brain MRI may help
• Therapy: in CS, carbidopa-levodopa has helped with some tremors but this has not been used as much in XP to date
en.wikipedia.org
Ataxia

• Problems with balance and coordination
• Typically arise from dysfunction in a part of the brain called the cerebellum
• Symptoms may include tremors with movement, frequent falls, balance problems while walking, difficulties with utensils, difficulties with writing and other fine motor activities
• Diagnosis: physical examination, sometimes supported by brain MRI findings
• Therapy: physical therapy and occupational therapy
Summary of neurological complications

• Most important component of monitoring is a periodic physical examination by a neurologist
• Serial brain MRIs may be useful but if sedation is needed that may necessitate adjustment of MRI surveillance
• A baseline EMG may be helpful, but serial EMGs usually not needed unless there are new or changing neuropathy symptoms
• Routine EEGs are not needed unless there is a concern for seizures
• Available treatments are primarily supportive and can have a significant impact on overall function and quality of life
Our biorepository
What is a biorepository?

• It is a collection of data and tissue samples that can be used for future research

• Data
  • Medical records
  • Family stories

• Tissue samples
  • Saliva
  • Blood
  • Fibroblasts (from skin biopsies)
Our biorepository

• Given the rarity of XP and other DNA repair disorders, it is difficult to amass the data and tissue samples needed to conduct statistically powered retrospective studies in a single clinic
• Thus we welcome participation by any affected individual
• We can consent and enroll any individual with a DNA repair disorder and sometimes other family members
• When possible we try to collect both data and a tissue sample (blood)
• If it is not possible to collect blood, we still find data to be helpful
• THANK YOU to all who have already enrolled in our biorepository
Natural history study
What is a natural history study?

• A prospective study that measures certain variables over time
• Once consented and enrolled, a participant is studied at multiple timepoints
• There has been no prospective natural history study of the neurological outcomes of XP
Why do a natural history study for XP?

• The disease course is complex and it would help us know what problems arise at different ages that we need to tackle

• To treat the neurological complications of XP, we have to find and validate a good outcome measure (measurement that represents a key part of the disease that we hope will improve with the therapy)

• We need natural history data and good outcome measures to test new therapies in clinical trials

• Senolytic therapies: Laura Niedernhofer and Paul Robbins

• Gene therapies: Christina Pacak
Outcome measures

• Is the therapy linked biologically to the outcome measure?
• Does the outcome measure capture relevant clinical features?
• Is the outcome measure free from bias?
• Will the outcome measure capture the expected degree of change?
  • Consider scale and sensitivity
  • Avoid ceiling effects
• Potential sources of data
  • Performance-based measure
  • Patient-reported outcome (PRO)
  • Third-party respondent (caregiver or professional)
• When should the outcomes be measured?
• Coster WJ, Am J Occup Ther 2013;67:162-170
Outcome measures in pediatric rare diseases

• Careful studies are needed to determine the optimal outcome measures for individual pediatric diseases
• Definitely not a “one size fits all” situation
• Different milestones are expected at different ages
• Manifestations and progression vary significantly depending on the specific disease and subtype
• Many potential outcome measures are not likely to change during the course of a clinical trial in the setting of a chronic disease
Potential outcome measures for XP

• MRI changes – cochlear implants and need for sedation in some individuals present barriers to adoption
• Tremors – will need a means of quantifying
• Nerve conduction studies and electromyography – may be consistent and reliable, but correlation to disease manifestations will need to be established
• Multi-item functional scales – none fully validated to date for XP
Primary versus secondary outcomes

• Primary outcomes determine ultimate conclusion
• Secondary outcomes are supportive, help interpret primary outcome
• More outcomes are not necessarily better
• Negative outcomes can confuse interpretation and hurt chances of drug approval
Our natural history study

• Cohort size: up to 40 affected individuals and 40 unaffected siblings
• Three major DNA repair disorders: XP, CS, TTD
• Follow specific outcome measures: ideally annually but with variability
  • Clinical outcome measures: Molly Stark
  • Biological outcome measures: laboratory studies
• The goals of a natural history study are
  • To improve patient care
  • Understand disease mechanisms better
  • To identify reasonable outcome measures for a clinical trial
• Do we look for improvement or stabilization with a new treatment?
• THANK YOU to all who are participating in our natural history study
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