Ultra-rapid genomic diagnosis offers treatment options for Wolman Disease and also reveals complex underlying genetic mechanism

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Background

• Deficiency of lysosomal acid lipase (LAL) - prevalence of 1 in 500,000 ¹
• Spectrum ranging from infantile-onset WD to later-onset cholesterol ester storage disease (CESD) ²
• CEs & TGs build up – leading to faltering growth, vomiting, steatorrhoea with diarrhoea and abdominal distension, can progress to anaemia and thrombocytopenia ¹⁻⁴
• Subcapsular adrenal calcifications- pathognomonic ⁵
• Was universally fatal in childhood until 2015 when ERT with sebelipase alfa was approved for use in the USA and EU ⁶
• Recent clinical trials of ERT with or without haematopoietic stem cell transplant have resulted in long term survivors of early onset forms ⁶,⁷

Case report – presentation

• 2-month-old infant presented with FTT, fever and lethargy, abdominal distension with marked hepatosplenomegaly
• Investigations:
  • sterile CSF pleocytosis
  • pancytopenia
  • Hyperferritinaemia
• Haemophagocytic lymphohistiocytosis (HLH) due to progressive sepsis and liver failure
• WD was suspected due to marked adrenal calcification on chest X-Ray with HLH a known secondary association

Image 1: Chest XRay showing marked adrenal calcification (arrows)
Genetic Results

• Rapid genomic sequencing AGHA Acute Care Project
• Within four days trio WGS: homozygous likely pathogenic missense variants in LIPA: c.524A>C; p.(Gln175Pro)
• Further analysis - paternally inherited chromosome 10 paternal isodisomy.
• WD not previously reported from UPD, recognised as cause for other autosomal recessive conditions

HLH and WD

• HLH described in several cases of WD
• Age of onset two weeks to twenty-one months, mostly around three months
• CEs form crystals which activate the inflammasome resulting in sustained acquired HLH
• Loss of cholesterol for steroidogenesis can lead to adrenal insufficiency

The diagnosis of HLH can be established if either 1 or 2 below is fulfilled:

1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH are fulfilled (five out of the eight criteria below):
   1. Fever
   2. Splenomegaly
   3. Cytopenias (affecting ≥ 2 lineages in the peripheral blood):
   - Hemoglobin <90 g/L (in infants<4 weeks: hemoglobin <100 g/L)
   - Platelets <100,000/μL
   - Neutrophils <1000/μL
   4. Hypertriglyceridermia and/or hypofibrinogenemia:
      - Fasting triglycerides ≥ 265 mg/dL
      - Fibrinogen ≤ 1.5 g/L
      - Hemophagocytosis in bone marrow or spleen or lymph nodes
   5. Low or absent NK-cell activity
   6. Ferritin ≥ 500 μg/L
   7. Soluble CD25 ≥ 2400 U/L

Supportive clinical criteria include neurologic symptoms and cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia, and transaminitis, hypoalbuminemia and hyponatremia

Image 2: Table showing the Diagnostic criteria for HLH from
ERT and Outcome

- International experts were consulted on the management of WD
- Treatment with sebelipase alfa ERT initiated
- Due to issues with fat metabolism, avoided intralipid, ceased breastfeeding and low fat formula Vivonex T.E.N introduced
- Etoposide ceased, high dose dexamethasone continued
- Two doses of weekly ERT administered
- Progression of illness – fulminant liver failure, hyperammonaemia and sepsis, coagulopathy, portal hypertension and refractory gastrointestinal bleeding
- Two and a half weeks after diagnosis the infant died, aged 3 months due to underlying critical illness

Conclusion

In this case ultra-rapid genomic sequencing led to a diagnosis of WD enabling treatment with ERT. The case also highlights the association of WD with HLH. Furthermore, the genetic mechanism of uniparental disomy was identified.

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References


