

# Wolman's Disease

Case Presentation in Genetics and Ethics

By Julie A. Nelson, R.N.C., W.H.C.N.P.-B.C.

# Wolman's Disease<sup>1</sup>

- Definition: It is a lysosomal storage disorder which causes a buildup of lipids in body organs and calcium in the adrenal glands.<sup>1</sup>
- Common symptoms in infants who are affected include enlarged liver and spleen, poor weight gain, low muscle tone, jaundice, vomiting, diarrhea, developmental delay and poor absorption of nutrients.<sup>1</sup>
- Symptoms begin shortly after birth and most infants do not survive past age one from malnutrition.<sup>2</sup>

# Wolman's Disease

- Estimated to occur in 1 in 350,000 newborns<sup>1</sup> (Over 50 cases of the disease have been reported)
- Autosomal recessive inheritance<sup>1</sup>
- Lipid storage disease<sup>2</sup>
  - These types of diseases are caused by the accumulation of lipids in the body because of a lack of enzymes needed to break down several types of lipids are not present or do not work correctly.
  - Over time these lipids accumulate in the bodies tissues and cause permanent cellular and tissue damage to the peripheral nervous system, liver spleen, adrenal glands, and the bone marrow.

# Related Conditions<sup>2</sup>

- Gaucher disease (most common)
- Nieman-Pick disease
- Fabry disease
- Farber's disease
- Gangliosidosis type 1 and 2
  - Tay-Sachs disease
  - Sandhoff disease
- Krabbe disease
- Metachomic leukodystrophy
- **Wolman's Disease**
- Cholesterol ester storage disease
- Hurler syndrome
- Pompe Disease

# Diagnosis

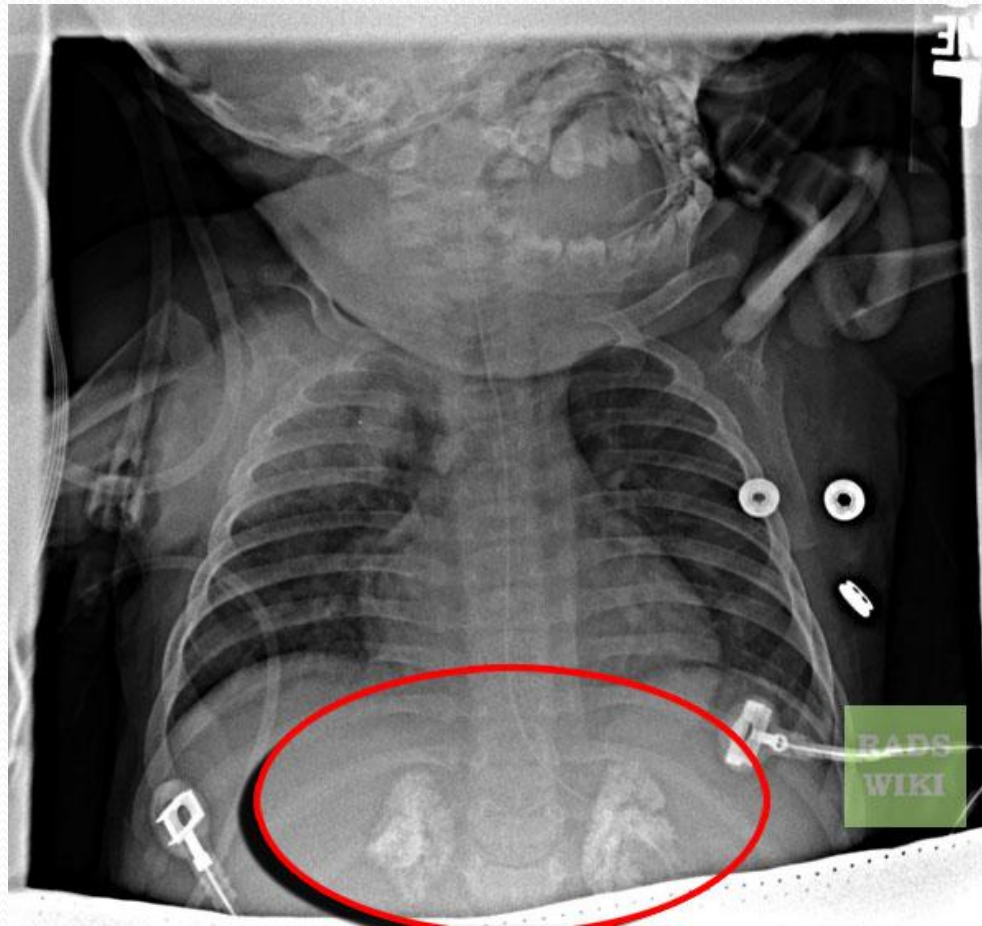
- Prenatal diagnosis is possible
  - According to a study of 111 CVS (chorionic villi samples) obtained at about 8-10 weeks of gestation. Various lysosomal storage disorders were identified by various ultrastructural features (31 of the 111) in high risk individuals were discovered on CVS examination.<sup>3</sup>

Diagnosis by leucocyte acid lipase estimation which can also be done on the parents of the child with the disorder. To evaluate they have half the function normally expected.<sup>4</sup>

# Clinical Diagnosis

- Patient usually present in the first weeks of life with failure to thrive, anemia, hepatosplenomegaly, steatorrhea, and enlarged calcified adrenal glands. Vomiting, abdominal distention, and jaundice is often present prior to obvious enlargement of organs.
- Further evaluation of the infant will most likely show calcifications of the adrenal glands as well as hepatosplenomegaly and abdominal distention.

# ADRENAL CALCIFICATIONS COURTESY OF RADS.WIKI



# Diagnosis continues:

- Diagnosis is made by the demonstration of the deficient cellular activity of lipase (which is cultured in skin fibroblasts or lymphocytes).
- Lipid profiles are usually normal.
- Storage of cholesterol esters produces foam cells in the liver, adrenal cortex, spleen, intestine, lymph nodes, circulating leukocytes, bone marrow, and central nervous system.
- When bone marrow aspiration shows foam cells containing large lysosomal vacuoles engorged with cholesterol esters and no cholesterol ester activity is found in fibroblasts, leukocytes, or marrow cells.



# Genetics of Wolman Disease

- Wolman's Disease is an autosomal recessive condition.
- The disease is completely penetrant with lethal allele and rapidly progressive to death (within weeks to months of birth) of affected individual.
- When both parents of the affected individual (proband) are tested they have half of the activity of lysosomal acid lipase than expected.
- Mutations in the LIPA gene cause Wolman Disease
  - LIPA gene provides instruction for producing an enzyme called lysosomal acid lipase.

# The LIPA Gene

- Mutations in the LIPA gene cause Wolman Disease
  - LIPA gene provides instruction for producing an enzyme called lysosomal acid lipase.
  - In normally functioning cells this enzyme is found in the lysosomes (which function to digest and recycle materials within the cells), where they process lipids such as cholesterol esters and triglycerides so they can be used by the body.

# Wolman Disease

- Mutations in this gene lead to storage of lysosomal acid lipase and the accumulation of cholesterol esters and other types of fats within the fats and tissues of affected individuals.
- This accumulation as well as the malnutrition caused by the bodies inability to use lipids properly results in the signs and symptoms of Wolman disease.

# The LIPA gene<sup>1</sup>

- Officially known as the lipase A, lysosomal acid, cholesterol esterase.
  - When cholesterol esters (cholesterol which is attached to a fatty acid) it is usually broken down by lysosomal acid lipase into a cholesterol and a fatty acid and excreted or used by the body as a nutrient. **(NORMAL FUNCTION)**

# Mutations of LIPA gene<sup>1</sup>

- In Wolman disease more than 10 mutations on the LIPA gene have been found to cause the disease.
- Most of the mutations cause production of an abnormally short version of lysosomal acid lipase, which does not function properly to break apart the cholesteryl esters formed within the cells. **(ABNORMAL FUNCTION)**

# Location of LIPA gene<sup>1</sup>

- The LIPA gene is located on the long (q) arm of [chromosome 10](#) between positions 23.2 and 23.3.
- More precisely, the LIPA gene is located from base pair 90,963,308 to base pair 91,001,639 on chromosome 10.

# Current Genetic Testing<sup>9</sup>

- Baylor College of Medicine and several other specialty labs around the United States
  - Medical Genetics Laboratories
    - Houston, Texas

Testing offered:

Analysis of entire coding region  
sequence analysis  
enzyme assay  
prenatal diagnosis  
carrier testing

# Current Research<sup>7,8</sup>

- Research for treatments
  - Cincinnati STAR Center for Lysosomal Diseases is one of the only groups in the world studying the “mouse model” which has the genetic changes and physical symptoms found in these disorders.
  - Focus of research includes dose, effect and safety of enzyme replacement therapy in the mouse model.
  - Hopefully these studies will lead to the development of an enzyme replacement to treat these disorders.
  - 3 separate studies are active through [clinicaltrials.gov](https://clinicaltrials.gov)



# Treatment<sup>5</sup>

- The only long-term treatment of Wolman's Disease that has been found is four cases of hematopoietic cell transplantation (HCT) which has been reported to prevent hepatic failure and death.<sup>4</sup> (Bone marrow transplant).
- The longest survivors after stem cell transplant have been 4 and 11 years after transplant.

# After Bone Marrow Transplant<sup>5</sup>

- Survivors showed resolution of diarrhea several weeks after transplantation, normal hepatic function, improved hepatosplenomegaly and one returned to normal adrenal function as well.
- The youngest of the two, has also made age-appropriate neurodevelopmental and adaptive milestones and has no neurocognitive deficiencies.

# Ethical Dilemma

- Debbie is a 38 year old female who is pregnant with her first child. She is accompanied by her husband Paul. They did screening for birth defects at 12 weeks with Nucal Cord thickness as well as periodic sonograms for evaluation of advanced maternal age. On SQ Heparin for management of multiple miscarriages.
- Debbie is at 28 weeks gestation and asks if she should collect her cord blood in a private or public blood bank. A close friend of the couple has been discussing cord blood banking through one of the private blood cord blood banks and the couple asks your opinion.

# Discussion with Debbie

- As her provider, you discuss what she has learned about the company. She states that the web sites shows that cord blood has been used to treat over 70 abnormalities and she feels this is a good reason to donate her babies cord blood for future use.
- She does not have any other risk factors and plan to attempt to have more children in the future. She has a long history of infertility and has taken 15 years to get pregnant so another pregnancy is unlikely.

# Ethical Debate

- Public versus Private Cord Blood Banking<sup>10</sup>
  - Private Cord Blood Banking: Provided in the United States by several different companies who market benefits of private blood banking to prospective parents.
    - Companies such as ViaCord, or Cord Blood Registry, or CryoCell.
    - Initial cost about 1500-2000 per collection
    - Yearly storage fees about 150-200 per year.
  - Promoted by private companies as “biological insurance” to be used if a stem cell transplant is needed

# Public Cord Blood Banking<sup>10</sup>

- Public Cord Blood Banking: In 2005, Congress passed the Stem Cell Therapeutic and Research Act
- This act provides a nationally funded *public* resource for the collection and maintenance of human cord and blood stem cells for treatment of patients and research.
  - Available to any patient requiring transplantation at no cost.
  - Not reserved for a person's private use.
  - Available for storage for any individual who has a first-degree relative that has a condition that will benefit from transplantation.

# Ethical Considerations

- Beneficence<sup>11</sup>
  - It is important to benefit the patient as well as not provide them with false promises.
    - Current private, for profit, cord blood banks promote the need for “biological insurance” for their child in case the child should need a stem cell transplant in the future for any of the almost 80 disorders that can be treated using cord blood transplantation.
    - These statements are based on the assumption that the cord blood sample banked will be able to be used for that infant for any of these disorders as stated by cord blood banks.

# Ethical Considerations

- Nonmaleficence-first do no harm.
  - It is unknown if quality control procedures are followed by all private banks, and if these banks will remain financially healthy for the duration of the child's life.
    - If the quality and stability is not assured potential harm could occur.
- Autonomy-The right to choose by informed consent
  - Providing for a choice can be promoted by informed decision making for either choice.



# For and Against

- *Against recommending* private cord blood banking
  - Beneficence-Recommendation regarding family's best interest is against private cord blood banking
  - Veracity-Recommendations should include distinct discussions about the realistic treatments that could and have recently occurred in autologous cord blood collection through private banking.
  - Nonmaleficence-giving false hope of possibility for the use of privately collected cord blood samples
- *For Recommending* private cord blood banking
  - After continued discussion-Respect for autonomy and yielding to the Debbie's decision regarding collection.

# Ethics Continued

- Deception- After careful consideration of the information given to patients by the private cord blood collection companies it is clear that there is deception in their presentation of the information and the actual benefit found from private cord blood donation.
- Veracity-defined as comprehensive, accurate, and objective transmission of information, as well as how the provider fosters the patient's or subject's understanding.<sup>13</sup>

# Current Opinion

- *ACOG<sup>14</sup>-(American College of Obstetricians &Gynecologists)*
  - Although ACOG takes no position for or against cord blood banking, it recommends that physicians disclose that there is no reliable estimate of a child's likelihood of actually using his or her own saved cord blood later.
  - Pregnant women should be aware that stem cells from cord blood cannot currently be used to treat inborn errors of metabolism or other genetic diseases in the same individual from which they were collected because the cord blood would have the same genetic mutation. "Cord blood collected from a newborn that later develops childhood leukemia cannot be used to treat that leukemia for much the same reason."

# World Marrow Donor Policy<sup>12</sup>

- Utility of Autologous for Family Cord Blood Unit Storage
  - Use of Autologous cord blood cells for the treatment of childhood leukemia is contraindicated because preleukemic cells are present at birth. Also the cord blood carries the same genetic defects as the donor and should not be used to treat genetic disease
  - There is no approved protocol where the autologous cord stem cells are used in therapy.
  - If these autologous stem cell therapies should be of use in the future, it will most likely be based on treatments with easily accessible stem cells.

# Other Opinion

- American Academy of Pediatrics (AAP)<sup>10</sup>
  - Because there is no scientific data at the present time to support autologous cord blood banking, private storage of cord blood for biological insurance is discouraged.
- Legal Issues-no known legal issues are present unless a provider could be implicated in the unfair promotion of a service that is not found to be as beneficial as once thought.

# Solution

- It is acceptable to give Debbie information regarding private cord blood banking as well as public donation.
  - Important to provide information regarding realistic use of autologous units.
  - Also important to provide information regarding the fact that this is a commercial venture on the part of the private cord blood bank.
  - Pros and cons of each type of cord blood banking should be discussed.
  - Patient should be allowed to reach her own conclusion with support of her decision by her provider.

# Debbie and Paul's Decision

- Debbie and Paul consider the information and decide to do public cord blood banking of their baby's cord blood at birth.
- They choose to use a CryoCell who offers collection of cord blood to be shipped to the company and donated for public use.
  - CryoCell also will do family donation for no fee if there is a sibling or close relative with a need for transplantation within the public donation parameters.
  - CryoCell has both public and private cord blood collection abilities and donations are accepted from the public.

# My Opinion

- Although private cord blood banking has been advertised as a great way to provide “biological insurance” the truth of the matter is that many of the claims of the private blood banking companies are misleading to the average parent.
- Unfortunately as providers we are obligated to bring a sense of veracity to discussions with our patients and their families and base recommendations on this truth.



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