International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Postmortem Diagnosis of Infantile Tay-Sachs Disease: A Case Report with Clinicopathologic Correlation

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Running Title: Infantile Tay-Sachs Postmortem Diagnosis

Abstract: ***Tay Sachs disease is a rare autosomal recessive neurodegenerative disorder caused by a deficiency of the lysosomal enzyme β hexosaminidase A, resulting in the accumulation of GM2 gangliosides in neurons. This case describes a 5-year-old bedridden girl with classical findings of Tay Sachs disease confirmed by clinical features, imaging, histopathology, and enzyme analysis. The hallmark histological feature-ballooned neurons with cytoplasmic vacuoles-was observed. This case underscores the importance of integrating histopathology and clinical correlation for diagnosis.***

Keywords: Tay Sachs disease, neurodegenerative disorder, ballooned neurons, hexosaminidase A, lysosomal storage disease

1. Introduction

Tay Sachs disease is a rare autosomal recessive lysosomal storage disorder resulting from deficiency of the enzyme β-hexosaminidase A, necessary for the degradation of GM2 gangliosides. This leads to progressive neuronal destruction, primarily affecting infants and young children. It has an incidence of approximately 1 in 320,000 live births worldwide and is particularly prevalent in Ashkenazi Jewish populations[1].

2. Case History

We report a case of a 5-year-old girl, found deceased in an orphanage, with a history of delayed developmental milestones and seizures since age 2. She had initially developed normally until the age of 1, after which her caregivers noted a regression in developmental milestones. Over time, she lost vision, developed severe motor weakness, dysphagia, and became non-responsive with no higher mental functions.

Neurological examination revealed poor motor coordination, absence of reflexes, sagging skin of the lower limbs, and significant swelling in the genital area.

Investigations included:
- MRI Brain: Mild prominence of cerebellar folia and unmyelinated periatrium white matter
- Visual Evoked Potential (VEP): Absent
- Brainstem Evoked Response Audiometry (BERA): Absent
- Fundoscopy: Cherry red spots in both eyes

Metabolic Screening:
- Aminoacidopathy panel: Normal
- Fatty acid oxidation disorder: Normal
- Enzyme assay:
- Hexosaminidase A: <5% (↓)
- Total Hexosaminidase: <10% (↓)
- Chromosomal Study: Normal
- Other findings: No significant amino acid or organic acid abnormalities

Autopsy findings
- Brain: Shrunken with prominent sulci and gyri
- Lungs: Pleural cavity filled with red fluid; left lung adherent to diaphragm; lower lobe of left and middle and lower lobes of right lung consolidated
- Kidneys: Dilated calyces
- Other organs: Pale

Histopathology
Microscopic examination of the brain revealed ballooned neurons in the cerebral cortex with cytoplasmic vacuolation. Special staining (Oil Red O) showed distended lysosomes with ganglioside accumulation. Other organs (lungs and kidneys) showed evidence of lobar pneumonia and features of acute pyelonephritis, respectively.

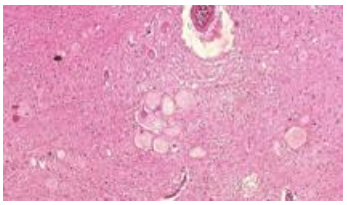

Figure 1: (100X)

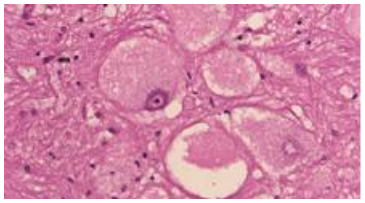

Figure 2: (400X)

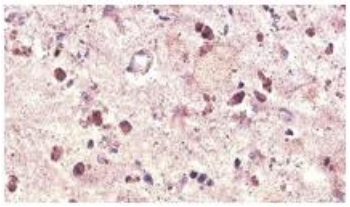

Figure 3: (Oil red O)

Fig 1 and 2 H &E shows ballooned neurons in cerebrum with cytoplasmic vacuoles. Fig 3 Special stain with Oil red O showing positivity.

3. Discussion

Tay Sachs is caused by mutations in the HEXA gene, resulting in deficient hexosaminidase A, which leads to the accumulation of GM2 gangliosides in neurons and progressive neurodegeneration[2]. The disease is common among Ashkenazi Jews but also occurs sporadically in other populations. It typically presents within the first year of life with:

- Developmental delay
- Hypotonia
- Exaggerated startle response
- Visual loss with cherry-red spots on fundus exam
- Seizures and paralysis
- Death by 4–5 years, often due to infections[3]

Histologically, neurons show vacuolated cytoplasm representing distended lysosomes filled with lipid material, ballooned neurons which are classic. This is caused by lysosomal storage of gangliosides[4]. Sudan black B, Oil Red O, and PAS stains are positive due to lipid accumulation[5]. On electron microscopy, a whorled pattern (onion skin) may be observed in lysosomes. The clinical picture in this case — progressive neurological deterioration, seizures, cherry red maculae, and absent reflexes — is typical of infantile Tay-Sachs disease. Diagnosis was supported by deficient enzymatic activity. The postmortem histology confirmed the neuronal storage disorder.

This case underlines the necessity of considering lysosomal storage disorders in children with unexplained neurodegeneration, especially when systemic signs such as cherry red spots and seizure disorders are present.

Differential diagnoses include other lysosomal storage disorders (Sandhoff disease, Niemann-Pick disease), but enzyme assays help confirm diagnosis[6].

4. Conclusion

Infantile Tay-Sachs disease, though rare, should be suspected in infants with developmental regression and neurological decline. Postmortem examination and enzyme assays remain crucial for confirmation in settings where early clinical diagnosis is missed. Awareness of the histopathologic hallmarks is essential for pathologists and clinicians alike.

Informed Consent: As this is a postmortem study with anonymized data, consent exemption was granted by the institutional ethics committee.

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