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Ultrastructural alterations of renal tissue in a male patient with Fabry's disease

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ABSTRACT

Background: Fabry's disease is an X-linked lipid storage disorder due to deficient lysosomal alpha galactosidase A.

Case Presentation: Kidney biopsy was done on a 19 year old male patient with complaint of acroparesthesia, maculopapular skin lesions and cornea verticillata. Kidney biopsy tissue was processed and examined by electron microscopy. Changes were inclusion bodies in the cytoplasm of the renal cells. These inclusions were osmophilic with concentric lamellation of clear and dark layers, showing onion skin appearance. The podocytes were mostly affected and some of the foot processes were fused. Cross-sections of collagen fibers were also evident, indicating fibrosis.

Conclusion: The ultra-structure of the kidney clearly showed the intra-cytoplasmic glycosphingolipid accumulation in renal cells, responsible for progressive decline in renal function which could lead to kidney failure. The final diagnosis of Fabry's disease was confirmed. In the present case-study, electron microscopy proved to be a valuable diagnostic aid.

1. Introduction

Fabry's disease is an X-linked lipid storage disorder due to deficient lysosomal alpha galactosidase A. In this disease dermatological and soft tissue symptoms, angiokeratomas are common skin lesions which appear in adulthood and are considered as a significant diagnostic value.[1] Cornea verticillata was noted in 94.1% hemizygotes and 71.9% heterozygotes patients and considered as an ophthalmological indicator of this disease.[2] Globotriaosylsphingosine was identified as a bioactive molecule accumulating in Fabry's disease, which could modulate the release of secondary mediators of injury in podocytes.[3] High doses of agalsidase showed to have effects on the clearance of inclusion bodies in epithelial cells of distal tubules as well as podocytes.[4] Incidence of the disease has been estimated to range from one per 40,000 to one per 117,000 male live births. The gene for this disorder is on the X-chromosome and the mother needs to be a carrier to produce an affected child.[5,6] Mean survival is 40–50 years for males and 70 years for female carriers, death occurs from cardiac, renal, or cerebrovascular complications.[7] Kidney is affected in all hemizygous male. Renal pathological and functional impairment is more evident in hemizygous males than heterozygous females.[8] Studies revealed greater podocyte vacuolization in male patients than in female ones.[9] Progressive intracellular deposition of glycosphingolipid which ultimately leads to end-stage renal failure.[10–12] By light microscopy, distinctive "Foamy" cytoplasmic alterations were observed in renal glomerular, tubular, vascular, and interstitial cells.[13–15] Large amounts of lipid material are seen in podocytes followed by parietal epithelial, mesengial and glomerular endothelial cells.[16] Immunohistochemical localization of glycosphingolipid was also documented.[17] Other methods failed to reveal small amounts of stored glycolipid.[18] Kidney biopsy is of importance in evaluation of Fabry nephropathy.[9] Maltese cross particles, anti-CD77 antibody binding within vacuolated urinary epithelial cells were detected in Fabry disease.[19] Large numbers of electron dense deposits in the renal tubules was reported,[20] these deposits showed characteristic "onion skin" or "zebra appearance" in all kinds of renal cells.[15] Electron microscopic examination of kidney biopsy specimen is important for investigation of storage diseases.[21]

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2. Case report

Kidney biopsy was done on a 19 year old male patient with complaint of acroparesthesia, maculopapular skin lesions and corneal verticillata. Various investigations preformed on the patient are presented in Table 1, based on overall results, kidney biopsy was performed, tissues fixed and processed routinely and ultrathin sections of 60–70 nm were cut, stained with uranyl acetate and lead citrate and examined under TEM (Philips CM 100). The ultrastructural changes were mainly intracytoplasmic inclusion bodies in the renal cells, they were dense osmophilic with concentric lamellation of clear and dark layers, showing onion skin, zebra appearance and sometimes fingerprint like myelin figures (Fig. 1A). These electron dense deposits were more in the podocytes (Figs. 1B and 2A), they were also seen in the mesangial cells (Fig. 2B), and were found to be less in the tubular epithelial cells. Podocytes were most affected in these structures. In some places foot processes were found to be fused. Cross-sections of collagen fibers were also evident in different parts, indicating fibrosis.

Table 1
Summary of investigations.

Investigations	Results
Skin biopsy	Angiokeratoma corporis diffusum
EMG/NCV	Normal
Sonography	Abdomen: normal Pelvis: normal
CT scan	Brain: normal Orbit: normal
Echocardiography	Normal
Spirometry	Normal
Ophthalmoscopy	Cornea verticillata
Urine analysis	Hematuria

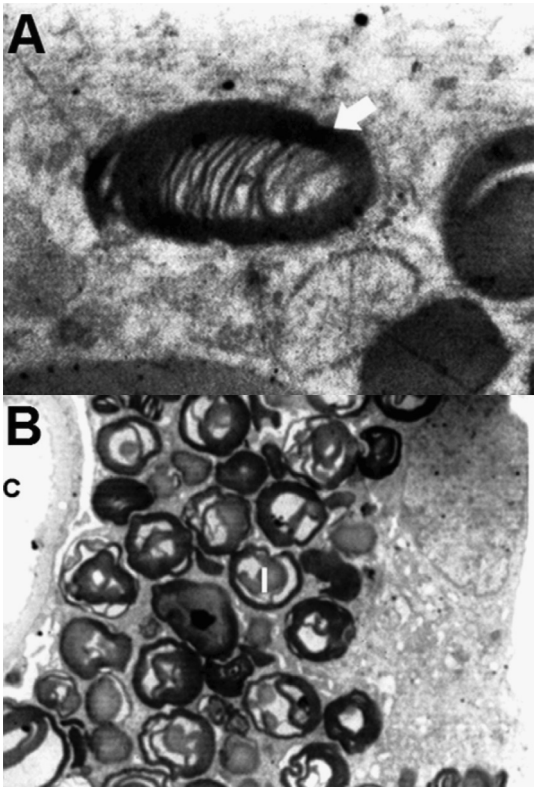

Fig. 1. A – Electron micrograph of intracytoplasmic osmophilic inclusion body (Arrow), showing fingerprint-like myelin figures (Original magnification ×13,500). B – Dense osmophilic inclusion bodies (I) packed in the cytoplasm of a podocyte, capillary lumen (C) is seen (original magnification ×1850).

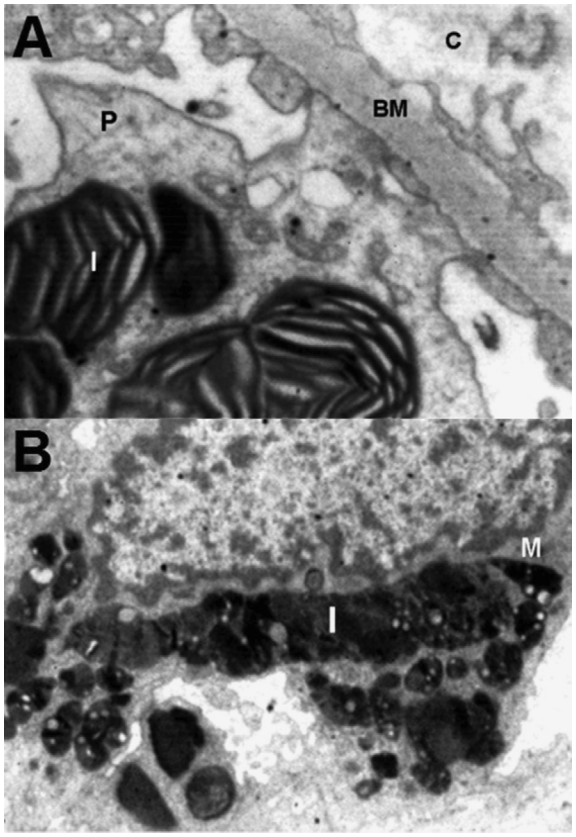

Fig. 2. A – Electron micrograph of a podocyte (P) with osmophilic inclusion bodies (I) in its cytoplasm which are typical onion skin or zebra appearance, basement membrane (BM) and capillary lumen (C) are also seen (Original magnification ×7400). B – Mesangial cell (M) with dense osmophilic inclusion bodies (I) in its cytoplasm (Original magnification ×3400).

3. Discussion

Intra-cytoplasmic accumulation of glycosphingolipid in the renal cells was clearly demonstrated, they were dense osmophilic concentric lamellar structures that would lead to kidney failure. Myelinosomes in great numbers were found in certain inborn errors of metabolism, these bodies have been given various names such as lipid cytosomes, multimembranous bodies, lamellar bodies, membranous cytoplasmic and zebra bodies. Myelinosomes containing stacked membranes and membranous whorls have been reported in kidney epithelial cells. Both the types of zebra bodies and whorl types were seen, which they were of zebra body types predominantly. In this case we observed most of these bodies in the podocytes and mesengial cells respectively and very minute in the tubular epithelium in contrast to the other reports in which large amounts of electron dense material was seen in the renal tubules.[20] This could be the reason in which we could not detect vacuolated epithelial cast in the urine analysis. Dysregulated autophagy in alpha-galactosidase A deficient mTOR kinase activity, which lead to deregulated autophagy pathways, opened a new horizon on pathogenesis of glomerular injury in Fabry disease.[21,22] Electron-microscopy is a far superior and easier way to diagnose these bodies than any other technique, however, light microscopy in which cytoplasmic changes in renal cells could be due to other lipid material could not be differentiated from glycosphingolipid,[13–15] on the other hand, when the amount of

glycosphingolipid is minute, even histochemistry will not be of diagnostic value.[18] In the present case-study, electron microscopy proved to be a valuable diagnostic aid.

4. Conclusion

The ultra-structure of the kidney clearly showed the intra-cytoplasmic glycosphingolipid accumulation in renal cells, responsible for progressive decline in renal function with which the final diagnosis of Fabry's disease was confirmed. In the present case-study, electron microscopy proved to be a valuable diagnostic aid.

Conflict of interest

Author states that there is no conflict of interest.

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