Hereditary Amyloid Polyneuropathy in a Family from North West India: Phenotypic, MRI and Pathologic Study

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Abstract
Hereditary amyloid polyneuropathies are rare, heterogeneous group of autosomal dominant disorders and deserve special attention because of its rare presentation, multisystem involvement and significant therapeutic implications if diagnosed early. We report a male patient of hereditary amyloid polyneuropathy from North West India with peripheral nerve, autonomic nervous system, vitreous and cardiac involvement.

Introduction
Myeloidosis is a term for diseases that are due to extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. Neuropathies in particular are commonly seen in primary (AL) and hereditary amyloid polyneuropathies (Familial amyloid polyneuropathies) (FAP), while it is rare in secondary (AA) amyloidosis except patients on long term dialysis. Hereditary amyloid polyneuropathies are classified in four types based on clinical presentation. In modern classification, FAP is divided into three types based on abnormal constituent protein (transthyretin (TTR) related, apolipoprotein A-1 related and gelsolin related).¹ TTR-related FAP is most common FAP throughout world and more than 100 TTR mutations are recognised.⁶

Case Report
A 36 year old farmer presented with insidious onset progressive sexual (erectile) dysfunction and decreased sweating over feet of 3 years duration. He had difficulty in micturition in the form of increased effort and frequency, dry mouth, weight loss and progressive painless diminution of vision in both eyes over last 1 year. He was asymptomatic in upper limbs. There was no history of oculomotor, facial or bulbar weakness. There was no significant history of any medical illness in past. He took some ayurvedic medicines in past for sexual dysfunction. He was married, having three children, occasional alcoholic. He was born to nonconsanguineous parents and his family history revealed affection of other family members with similar complaints (Figure 1).

On examination, his pulse rate was 84/min., regular; BP in supine position was 130/80 mmHg and in standing after 3 minutes was 100/60 mmHg. General examination was normal except burns over both legs due to steam application. He was conscious, co-operative, well oriented and higher mental functions were normal. Visual acuity was 6/60 and fundus could not be visualised due to hazy media in both eyes. Motor Power was normal at all joints except ankle dorsiflexion and plantar flexion was 4/5. Deep tendon reflexes were normal except absent ankle jerks. Plantars were mute. He had loss of pain and temperature sensation in both legs up to knees with intact touch, joint position and vibration sense. His bilateral ulnar and peroneal...
nerves were thickened. Autonomic function tests revealed impaired heart rate response to breathing and standing along with postural drop of BP 30/20 suggestive of both sympathetic and parasympathetic nervous system involvement.

His haemogram revealed Hb 10.4 gm/dl and ESR 50 mm 1st hr. Urine analysis including 24 hr urine protein was normal and urine porphobilinogen was negative. Serum biochemistry revealed normal renal function test, liver function test, thyroid profile, blood sugar and glycosylated haemoglobin. His ELISA for HIV, VDRL, HBsAg and vasculitic profile including ANA, Anti ds DNA, CRP, RA factor, Ss-A/Ro and Ss-b/La antibodies were negative. X ray chest and USG abdomen were within normal limits. 2D echocardiography revealed granular sparkling appearance of myocardium especially in septal region.

Motor nerve conduction studies revealed decreased CMAPs and nonrecordable F waves in bilateral common peroneal and tibial nerves and prolonged distal latencies in median nerves. Bilateral sural nerve SNAPs were nonrecordable with delayed onset latencies of median sensory conduction studies. So there was suggestion of sensorimotor axonal involvement of lower limb nerves and early demyelinating affection of bilateral median nerves. Symaptic skin response was absent from lower limb suggestive of autonomic neuropathy in lower limbs.

MRI of brain and spine was normal. Skin biopsy from dorsum of foot was inconclusive without any evidence of epitheloid cells or AFB. Right Sural nerve biopsy showed pale eosinophilic amorphous material around endoneurial capillaries which gave metachromatic staining with crystal violet confirming amyloidosis (Figure 3). Subsequently rectal mucosa biopsy was also positive for amyloidosis (Figure 2). His muscle biopsy from quadriceps and abdominal fat pad biopsy specimen did not reveal presence of amyloid material. Patient underwent vitrectomy, following which his vision improved.

Subsequently two of his paternal cousins undergone vitrectomy for complaints of diminution of vision. Vitreous fluid examination of one of them revealed presence of amyloid material by congo red staining.

**Discussion**

Familial amyloid neuropathies are a heterogeneous group of autosomal dominant disorders characterised by deposition of a fibrillar protein with abundant beta pleated structure in extracellular space. Familial amyloid neuropathy can be classified into three types according to abnormal protein (TTR, apolipoprotien-A1, gelsolin) of which TTR amyloidosis is most common type. Diagnosis of FAP requires demonstration of amyloid material in biopsy, immunohistochemistry for characterisation of abnormal protein and detection of mutation. In our case presence of characteristic clinical features, family history and demonstration of amyloid material in biopsy leaves no doubt about diagnosis of FAP. However characterisation of abnormal protein could not be done, due to lack of immunohistochemistry and genetic analysis facilities.

On the basis of onset and clinical features FAP can be divided into four types. Type 1 is most common form characterised by lower limb onset

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**Fig. 1 : Pedigree chart showing affection of other family members**
and multisystem involvement while type 2 is more restricted form and manifests with carpal tunnel syndrome. Type 3 is characterised by duodenal ulcers and early renal involvement. Type 4 manifests with cranial nerve involvement and corneal dystrophy.1 Our patient had features of type 1 FAP.

TTR amyloidosis has been recognised throughout the world, common in Portugal, Sweden, Japan and certain European countries. Of TTR related FAP types, ATTR Val30Met is the most common. Peripheral and autonomic neuropathy starts in second or third decade of life and average duration of illness is around 7-10 years. Clinical phenotype shows sensory disturbances starting from lower limbs, more pronounced for pain and temperature early in the course, followed by autonomic dysfunction, motor weakness and wasting. Cerebral involvement may occur due to deposits in the leptomeningeal and cerebral vessels. Other system involvement in form of restrictive cardiomyopathy, vitreous opacities and renal involvement is well documented.1,4 Our patient had evidence of peripheral nerve, autonomic nervous system, vitreous and cardiac involvement. There was no evidence of muscle, CNS or renal involvement in our case.

Histologic diagnosis of amyloid is based on its staining characteristics. For routine diagnosis, birefringence after congo red staining is the most widely practiced and reliable tool. Congo red under ordinary light imparts a pink or red colour to amyloid deposits. Under polarised light, the congo red stained amyloid shows a green birefringence. Confirmation can be obtained by electron microscopy. Other methods of differentiating amyloid from hyaline deposits include somewhat less specific histochemical techniques. For example amyloid stains metachromatically (violet or pink) with crystal violet or methyl violet.7 In our index case crystal violet staining was used to demonstrate amyloid material in nerve and rectal mucosa specimens (Figures 2, 3). But subsequently vitreous aspirate of his cousin revealed presence of amyloid material on congo red staining (sample was sent to other institute with facility of congo red staining).

Though data regarding FAP are abundantly present

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**Fig. 2 :** Microphotographs of rectal biopsy showing: a) low power showing normally arranged glands. A few vessels with thick walls are seen in the muscularis mucosae (arrow). (H&E, x100); b) high power view showing muscularis mucosae with pale eosinophilic material around blood vessels (H&E, x 400); c) Methyl violet stain showing metachromatic magenta staining in the material around blood vessels seen in (b)
in literature, most of it is from European countries. From India there are only two case reports describing clinical spectrum of FAP. One case reported from NIMHANS Bangalore, was that of young male without any family history presenting with peripheral nerve, muscle, vitreous, leptomeningeal and cardiac involvement.\(^2\) Another case reported from AIIMS New Delhi, was that of 35 years old female presenting with sensorimotor neuropathy, without any systemic involvement.\(^3\)

Various therapeutic approaches have been tried in cases of FAP, but only satisfactory modality so far is liver transplantation.\(^1\) Coutinho and colleagues proposed criteria that can be used for staging of disease preoperatively.\(^1\) Preoperative clinical severity and duration of illness influences the outcomes after liver transplantation.\(^3\) Some new drugs are under trial for treatment of FAP (diflunisal, tafamidis). Therefore a high index of suspicion is required for early diagnosis to consider liver transplantation and early vitrectomy which can significantly improve the vision.

### References


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**Fig. 3:** Microphotographs of sural nerve biopsy showing pale eosinophilic amorphous material around endoneurial capillaries. Material gave metachromatic staining with crystal violet.

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