An uncommon cause of bifacial weakness and non-length-dependent demyelinating neuropathy

Madhu Nagappa, Arun B. Taly, Anita Mahadevan[1], Mailankody Pooja, Parayil Sankaran Bindu, Yasha T. Chickabasaviah[1], Narayanappa Gayathri[1], Sanjib Sinha

Departments of Neurology and [1]Neuropathology, National Institute of Mental Health and Neurosciences, Bangalore, Karnataka, India

Abstract

Tangier disease is a rare metabolic disorder that causes neuropathy in half of the affected individuals. We present the clinical, electrophysiological, and histopathological findings in a middle-aged gentleman of Tangier disease who was initially diagnosed as leprosy and treated with antileprosy drugs. The presence of a demyelinating electrophysiology in a patient with predominant upper limb involvement and facial diplegia should raise the suspicion of Tangier disease. Estimation of serum lipids should form a part of routine evaluation in order to avoid misdiagnosis.

Key Words

Demyelinating neuropathy, facial weakness, tangier disease

For correspondence:
Dr. Arun B. Taly, Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore - 560 029, Karnataka, India.
E-mail: abtaly@yahoo.com

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Section 1

A 43-year-old male cook presented with difficulty in eye closure of 4 years duration that was associated with labial dysarthria. Over the last 3 years, he had noticed progressive difficulty in gripping objects with either hand, with thinning of forearms and painless burns over the distal upper extremities. He then developed numbness of the head and face, trunk, and upper limbs since a year. For these symptoms, he was prescribed presumptive anti-Hansen's treatment at another hospital. There was no history of visual or hearing impairment, positive sensory symptoms, or symptoms suggesting dysautonomia.

Examination revealed trophic changes with healed thermal burns over bilateral forearms and hands. In addition, there was bifacial weakness of lower motor neuron type [Figure 1B], distal hypotonia, wasting, and weakness of distal upper limbs. No ocular abnormalities could be identified on clinical and slit-lamp examination. There was markedly diminished sensation to temperature and pin-prick over the scalp, face, trunk, upper limbs, and proximal lower limbs up to mid-thigh [Figure 1A], reminiscent of a syrinx. Kinesthetic sensations and cerebellar system were intact. There was hyporeflexia, while the plantar responses were flexor bilaterally. There were no thickened nerves or anesthetic, hypopigmented skin patches. There was no family history of neuropathic illness.

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Questions to consider:
What are the key examination findings?

What are the differential diagnoses?

Section 2

The key findings in this middle-aged male patient included:
1. Bifacial weakness,
2. Distal bi-brachial weakness, and
3. An unusual pattern of dissociated sensory loss involving the face, trunk, upper limbs, and proximal thighs.

Bifacial weakness can arise from neuropathic and myopathic causes. Some of the neuropathic causes of bifacial weakness are listed in Table 1.

Hansen's disease, porphyria, Tangier disease, and sarcoidosis can cause neuropathy with a predominant upper limb

involvement [Table 2]. Neuropathy in Hansen's disease has a variable clinical course affecting the facial and peripheral nerves; this patient did not have thickened nerves as is commonly expected in Hansen's neuropathy. Porphyria causes a motor dominant neuropathy and is therefore considered an unlikely diagnosis in this patient. Neurosarcoidosis affects the facial nerve most commonly among the cranial nerves, and causes mononeuritis multiplex; this is a possible diagnosis despite the absence of cutaneous or other systemic markers. Tangier disease causes facial diplegia and peripheral neuropathy, which may be a mono- or polyneuropathy, with a variable clinical course.[1]

Other neuropathies associated with facial weakness were considered unlikely diagnosis in this patient because of clinical pattern of weakness and progression. Acute and chronic inflammatory demyelinating neuropathies are acquired immune-mediated disorders characterized by symmetric, ascending weakness of proximal and distal musculature, with the lower limbs being more severely affected. They may complicate human immunodeficiency virus (HIV) infection during the seroconversion phase. Facial palsy in Lyme's disease occurs in the acute stage and may be associated with radiculoneuropathy that resolves spontaneously over weeks to months even without specific treatment. Gelsolin familial amyloidosis is characterized by a triad of bifacial weakness, cutis laxa, and corneal lattice dystrophy. Neuropathy occurs late in the disease and is a sensory predominant neuropathy affecting the distal extremities first.[1]

Finally, the classical cause of dissociated sensory loss is syringomyelia; but the presence of facial diplegia and hyporeflexia in syringomyelia is rather exceptional. Tangier disease is known to present with dissociated pattern of sensory loss, the so called 'pseudosyringomyelic' pattern. The combination of bifacial weakness, upper limb weakness, and 'pseudosyringomyelic' pattern of sensory loss suggests a possible diagnosis of Tangier disease.[2,3]

Question

What investigation would you perform in this patient?

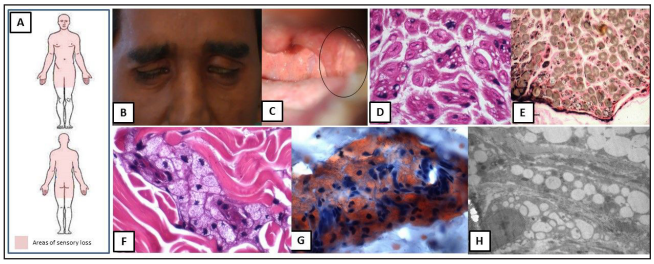

Figure 1: Schematic representation of distribution of reduced sensation to temperature and pain (A), and bifacial palsy resulting in incomplete eye closure (B). The color of tonsils is ambiguous (C). Biopsy of the sural nerve (D and E) shows vacuolation of Schwann cell cytoplasm (D) and mild depletion of small diameter myelinated fibers (F). Skin biopsy (F and G) shows bloated, vacuolated fibroblasts (F) that stain positively with Oil Red O confirming the lipid rich material (G). Electron micrograph reveals numerous lipid vacuoles in the cytoplasm of fibroblasts (H)

Section 3

Electrophysiological studies confirmed the presence of demyelinating neuropathy [Table 3], with absent sympathetic skin responses (SSR) from the palm and sole. Autoantibody profile (Euroline®, immunoblot technique), serum angiotensin converting enzyme levels (20.1 U/l; ref: 20-70 U/l), HIV antibody test, abdominal ultrasound, urine examination for porphobilinogen, and audiometry were normal. Lumbar cerebrospinal fluid (CSF) was normal except for mildly elevated protein (cell count: 0/mm^3; protein: 58 mg/dl, ref: 20-40 mg/dl; glucose: 61 mg/dl, ref: 40-60 mg/dl).

The lipid profilewas markedly abnormal viz. high density lipoprotein (HDL): 5 mg/dl (ref: 35-65 mg/dl), triglycerides: 185 mg/dl (ref: 50-150 mg/dl), total cholesterol: 149 mg/dl (ref: 110-220 mg/dl), very low density lipoprotein (VLDL): 37 mg/dl (ref: 10-40 mg/dl), and low density lipoprotein (LDL): 110 mg/dl (ref: 60-160 mg/dl). Serum apolipoprotein A1 was markedly reduced (<5.38 mg/dl; ref: 110-205 mg/dl). A diagnosis of Tangier disease was ascertained.

Tangier disease is a rare autosomal recessive disorder characterized by an abnormal accumulation of cholesterol esters in various organs secondary to adenotriphosphate binding cassette transporter A-1 (ABCA-1) deficiency and disrupted reverse cholesterol transport.[2,3] Neuropathy occurs in 50% of the patients with Tangier disease; the two clinical phenotypes include adult onset 'pseudosyringomyelic' pattern

Table 1: Neuropathy associated with bifacial palsy

Infectious	Lyme's disease Hansen's disease Human immunodeficiency virus (HIV) infection
Inflammatory	Acute inflammatory demyelinating polyneuropathy Chronic inflammatory demyelinating polyneuropathy
Granulomatous and connective tissue disorder	Sarcoidosis Sjogren's syndrome
Metabolic	Porphyria Tangier disease Diabetes mellitus
Inherited	Gelsolin familial amyloid neuropathy
Other	Neoplastic infiltration of skull base and meningeal diseases

Table 2: Differential diagnosis of non-length-dependent neuropathy

Guillain–Barre syndrome
Diabetes mellitus
Porphyria
Lead neuropathy
Hereditary amyloid neuropathy type II
Hereditary motor sensory neuropathy
Multifocal motor neuropathy with conduction block
Tangier disease
Sarcoidosis
Vasculitis

and relapsing-remitting mononeuritis multiplex.[2,4] Other manifestations include hepatosplenomegaly, ischemic heart disease, stroke, anemia, thrombocytopenia, corneal opacities, and asymptomatic detection following familial screening.[2] This patient did not have organomegaly on clinical or sonological examination of the abdomen. One of the major clinical signs is hyperplastic orange-yellow tonsils, which provides a simple bedside clue for etiology of neuropathy unless the patient has been tonsillectomized.[5] Diagnosis in nearly all children and adolescents is made by the presence of this characteristic tonsils, while neuropathy is the presenting feature in half the affected adults.[2] In our patient, the color of tonsils was ambiguous [Figure 1C]. Routine investigations including hemogram, erythrocyte sedimentation rate, and hepatic and renal function tests were normal. Slit-lamp examination for corneal fat deposits, Doppler of the neck vessels, and echocardiography were normal. Coronary angiogram was not carried out, as the patient was not symptomatic for ischemic cardiac disease.

A sural nerve biopsy performed elsewhere was retrieved and reviewed at our institute. It revealed mild depletion of small diameter myelinated fibers in small pockets in the periphery of each fascicle [Figure 1D and E]. In addition, there was a striking vacuolation of the Schwann cell cytoplasm indenting the nucleus [Figure 1D]. The histopathological finding of lipid accumulation in the Schwann cells is the possible histopathological correlate of demyelinating neuropathy on electrophysiological studies.[6] The lack of ABCA1 transporter responsible for transport of HDL cholesterol from various cells including the Schwann cells to plasma results in abnormal lipid accumulation.[7] It has also been hypothesized that focal nerve ischemia secondary to lipid accumulation also disrupts myelin and contributes to demyelination, slowed conduction velocity and conduction blocks.[8] Thus, Tangier disease forms one of the differential diagnosis of demyelinating neuropathy among other causes summarized in Table 4.

Skin biopsy revealed numerous bloated, finely vacuolated foam cells throughout the entire thickness of the skin, aggregating around the dermal capillaries, nerve twigs, and cutaneous adnexal structures. The vacuolated granular cytoplasm of these cells was seen indenting the nucleus [Figure 1F] and contained Oil Red O material, confirming the presence of lipid rich material [Figure 1G]. On electron microscopy, vacuoles were demonstrated distending the cytoplasm of cutaneous fibroblasts [Figure 1H].

In Tangier disease, abnormal lipids accumulate in several tissues including tonsils, liver, spleen, lymph nodes, thymus, gastrointestinal mucosa, bone marrow, and fibroblasts of the skin in Tangier disease. Cutaneous deposition of cholesterol esters has been demonstrated in clinically uninvolved skin in patients with Tangier disease.[9] Thus, skin biopsy is a valuable tool for diagnosis; it may also serve as a model for further research into the pathogenesis, development of newer drugs, and follow-up of patients with this rare disorder.[9]

The underlying genetic defect in Tangier disease is mutation in gene encoding ABCA1, a transmembrane protein that functions in transporting free cholesterol from peripheral tissues to ApoA1 or nascent HDL, which in turn is converted to HDL.

Table 3: Summary of electrophysiological findings

Nerve	Parameters	Control	Right side	Left side
Median	DL (ms)	3.1±0.6	5.05	5.2
	CMAP (mV)	7.0±3.0	5.56	5.16
	CV (m/s)	56.8±5.1	30.4	45.2
Ulnar	DL (ms)	2.0±0.5	5.45	6.8
	CMAP (mV)	10.9±2.6	4.27	3.56
	CV (m/s)	59.9±4.8	15.1	30.4
CP	DL (ms)	5.3±0.6	4.45	3.8
	CMAP (mV)	5.1±2.3	10.7	8.5
	CV (m/s)	51.2±3.7	41.7	44.1
PT	DL (ms)		7.55	5.55
	CMAP (mV)		3.21	3.52
	CV (m/s)		32.2	32.2
Median	SNAP (μv)	21.4±4.2	Absent	Absent
	CV (m/s)	59.8±4.5		
Ulnar	SNAP (μv)	22.5±6.7	Absent	1.5
	CV (m/s)	56.2±4.1		37.3
Sural	SNAP (μv)	28.5±3.6	Absent*	23.9
	CV (m/s)	48.8±3.8		44.0
SP	SNAP (μv)		40.0	15.8
	CV (m/s)		41.2	40.0

DL = Distal latency, CMAP = Compound muscle action potential, CV = Conduction velocity, SNAP = Sensory nerve action potential, CP = Common peroneal nerve, PT = Posterior tibial nerve, SP = Superficial peroneal nerve. *Right sural nerve biopsied

Table 4: Differential diagnosis of demyelinating neuropathy

Acquired	Acute/subacute/chronic inflammatory demyelinating polyradiculoneuropathy
	Multifocal motor neuropathy with conduction block
	Paraproteinemias
	Infections: AIDS, Lyme's disease, diphtheria
	Drugs and toxins: Amiodarone
Inherited	Hereditary motor sensory neuropathy (CMT 1, X)
	Hereditary neuropathy with liability to pressure palsy
	Metachromatic leukodystrophy
	Krabbe disease
	Adrenomyeloneuropathy
	Cerebrotendinous xanthomatosis
	Refsum's disease

AIDS = Acquired immunodeficiency syndrome, CMT = Charcot-Marie-Tooth disease

The gene for ABCA1 is located on chromosome 9q22-q31 and consists of 50 exons encoding a 2262-aminoacid-long protein.[2] More than 100 mutations have been described and they result in premature termination of protein translation and near total absence of ABCA1 expression. Majority of the mutations are missense mutations; nonsense and frame-shift mutations have also been reported.[2,10,11] The type and location of mutation in *ABCA1* gene may determine disease severity and is modulated by genetic background and environmental factors.[11] It is

interesting to note that clinical phenotype is inherited as an autosomal recessive trait, while the biochemical abnormality is autosomal codominant. Thus heterozygotes are symptomatic, lack clinical signs of neuropathy, but harbor lipid abnormalities that are intermediate between normal and Tangier disease.[2] Genetic testing could not be undertaken in our patient due to nonavailability of the facility at our center and economic constraints.

Question to consider

How will you treat this patient?

Section 4

The management of Tangier disease is essentially limited to dietary modifications with low fat content, prevention of physical injuries, and prevention and management of cardiac complications as no specific treatment is available. Newer experimental synthetic molecules including fatty acid bile acid conjugates (FABACS) such as aramchol that are designed to increase the reverse cholesterol transport have been explored; but current evidence suggests that they do not overcome the critical step requiring ABCD1 activity in reverse cholesterol transport.[12] Cholesterol ester transfer protein (CETP) inhibitors like dalcetrapib and reconstituted HDL may be considered pending the development of more effective therapies.[2]

Discussion

Tangier disease is a rare metabolic disorder; less than 100 cases are reported worldwide since the original description about half a century ago by Fredrickson from Tangier Island off the Chesapeake Bay. The combination of facial diplegia and predominant involvement of upper limbs is the characteristic clinical phenotype; this coupled with the typical lipid profile clinches the diagnosis of Tangier disease. A close differential diagnosis of neuropathy associated with reduced HDL, Apo-A1 related amyloidosis, can be distinguished clinically from Tangier disease by the presence of small fiber involvement, autonomic dysfunction, renal failure, and cardiomyopathy.[13]

Because of the pattern of sensorimotor deficits, and regional endemicity, our patient was initially misdiagnosed as leprosy, although the sural nerve biopsy and split skin smear did not show evidence of leprosy. The course in Tangier disease may be relapsing-remitting and may mimic an immune-mediated neuropathy clinically and electrophysiologically.[6,7] Patients presenting with clinical features of polyneuropathy or mononeuritis multiplex are likely to undergo skin biopsy as a part of diagnostic evaluation for vasculitis, leprosy, sarcoidosis, and amyloidosis. The presence of lipid accumulation in these peripheral tissues should be looked for in addition to the above differential diagnosis.

In conclusion, the presence of a demyelinating electrophysiology in a patient with predominant upper limb involvement and facial diplegia should raise the suspicion of Tangier disease. Simple biochemical tests in the form of estimation of serum lipids should form a part of routine evaluation in these patients in order to clinch the diagnosis. This will in turn avoid misdiagnosis and institution of inappropriate therapy.

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