Clinical and laboratory correlates of selective autonomic dysfunction due to Ross syndrome

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Introduction
Ross syndrome is characterized by the presence of the triad of segmental anhidrosis, depressed deep tendon reflexes, and tonic pupils. It is a rare, misdiagnosed autonomic disorder with less than 80 cases reported in the world literature. Two representative cases of Ross syndrome are presented with their laboratory correlates and relevant review of literature. Both cases (aged 35 and 58) presented with complaint of decreased sweating over one half of the face and ipsilateral upper limb and trunk and contralateral lower limb. There was compensatory increased sweating and hyperpigmentation over the remaining parts of the body. The duration of symptoms was 2 years and 15 days. The patients had variegated skin color as per the above distribution and hyporeflexia in lower limbs. One patient also had Holmes-Adie pupil. Iodine test showed hypohidrosis in the described areas, which was confirmed by skin biopsy in both cases. The patients were treated symptomatically with incomplete relief. The authors aim to highlight this rare disorder that can be one of the causes of pathological sweating encountered in general practice and the challenges in its management.

Keywords: Autonomic disorders, myotonic pupil, Ross syndrome, sudomotor

Case Reports

Case 1
A 58-year-old, middle-aged businessman presented with decreased sweating over the right half of the face, right upper limb and trunk, and left lower limb for 15 days with increased sweating and pigmentation over the remaining parts of the body. The duration of symptoms was 2 years and 15 days. The patients had variegated skin color as per the above distribution and hyporeflexia in lower limbs. One patient also had Holmes-Adie pupil. Iodine test showed hypohidrosis in the described areas, which was confirmed by skin biopsy in both cases. The patients were treated symptomatically with incomplete relief. The authors aim to highlight this rare disorder that can be one of the causes of pathological sweating encountered in general practice and the challenges in its management.

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Access this article online
Quick Response Code:  
Website: www.jfmpc.com  
DOI: 10.4103/jfmpc.jfmpc_151_19

How to cite this article: Panda S, Verma D, Budania A, Bharti JN, Sharma RK. Clinical and laboratory correlates of selective autonomic dysfunction due to Ross syndrome. J Family Med Prim Care 2019;8:1500-3.
sweating [Figure 2a, b] without any sensory loss. Hyporeflexia was noted in lower limbs.

**Case 2**

A 35-year-old man, mason by occupation, presented with decreased sweating over left half of face, upper back, and right lower limb for preceding 2 years with increased sweating over contralateral parts. No motor, sensory, bladder, or bowel involvement or other antecedent events were noted. Vital signs were normal. No peripheral nerve thickening was observed. There was hyperpigmentation over right half of face, lower back, and left lower limb with hypopigmented skin without loss of cutaneous sensation in the hypohidrotic areas described historically [Figure 2c, d]. There was hyporeflexia in both lower limbs.

In both patients, hematological and biochemical profile including complete blood count, erythrocyte sedimentation rate, blood glucose, glycosylated hemoglobin, liver, kidney, and thyroid profile was normal. Serology for syphilis, HIV, Hepatitis B and C was negative. Ultrasound of abdomen was normal. Ophthalmological assessment was unremarkable. Nerve conduction studies in both cases showed a mild degree of sensorimotor demyelinating polyneuropathy in lower limbs with absence of sympathetic skin response. Starch iodine test showed lack of color change in the hypopigmented areas suggesting hypohidrosis with bluish discoloration in remaining areas correlating with regions of hyperhidrosis. Autonomic function test was normal in Case 1, while it revealed reduced resting cardiac autonomic tone and reduced sympathetic reactivity (Ewing’s score 3) in Case 2. MRI of brain and spine was normal in both cases. Autoimmune profile autoantibody screen including anti-nuclear antibody, rheumatoid factor, anti-Sjogren syndrome related antigen A and B, and perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibodies were unremarkable. Skin biopsy with Fite stain was negative for lepra bacilli in both. However, there was focal flattening of rete ridges in epidermis and relative increase in eccrine glands at dermis and subcutaneous junctions in regions of hyperhidrosis and relative decrease in eccrine glands at lower dermis in the areas of hypohidrosis [Figure 3].

Symptomatic treatment with anticholinergic agents and avoidance of heated environments was given. An empirical trial of steroids was given in Case 1. There was transient decrease in hyperhidrosis, especially with the modification of the environment and gradual change in weather with onset of rains. However, steroids did not produce any further change. The second patient, being a mason worker, could not modify his environment and continued to have symptoms.

**Discussion**

Ross syndrome is a rare, misdiagnosed, benign progressive selective autonomic disorder.[1] The diagnosis is based on the demonstration of the classical triad of sudomotor defects, myotonic pupil, and hyporeflexia. It has no gender, ethnic, or age predisposition, though it predominates in the third decade. Harlequin, Holmes Adie, and Ross syndromes form a continuum. Ross syndrome may be incomplete or complete. While sudomotor involvement is mandatory, incomplete Ross syndrome has either or both absence of Adie pupil and hypo-/areflexia.[1,2] This rare disorder of sweating is associated with localized or widespread hypohidrosis/anhidrosis and compensatory hyperhidrosis. The hypohidrosis is considered to be caused by damage to postganglionic sympathetic fibres innervating sweat glands.[3] There is a reduced network of fibres not having receptors for vasoactive intestinal peptide (cholinergic) or dopamine-β-hydroxylase (noradrenergic) axons. In contrast, excessive sweating, a major distressing complaint that increases with exercise and hot weather, is compensatory in nature or due to loss of cholinergic M2 inhibitor presynaptic autoreceptors. This may eventually be lost giving way to anhidrosis. Adie’s tonic pupil

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**Figure 1:** (a and b) Holmes Adie pupil on right side in Case 1

**Figure 2:** (a and b) Variegated skin pigmentation corresponding with areas of hypo- and hyperhydrosis in Case 1; and (c and d) Starch Iodine test showed lack of colour change suggesting hypohidrosis in the areas described clinically to have decreased sweating in Case 2
A few reports suggested the role of autoimmune causation. Other conditions such as diabetes, leprosy, multisystem atrophy, and congenital insensitivity to pain with anhidrosis (type 4 and 5) may cause similar sudomotor symptoms leading to partial anhidrosis (hereditary sensory and autonomic neuropathy), atrophy, and congenital insensitivity to pain with anhidrosis or segmental dysautonomia, and lack of definite documented cure.

This case series brings focus on Ross syndrome, its peculiar segmental dysautonomia, and lack of definite documented cure. A greater awareness among family physicians, dermatologists, ophthalmologists, and neurologists and longer follow-up is required for better understanding of risk factors, pathogenesis, and difficulties in management.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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