Case Report

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

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Abstract

Ross syndrome is diagnosed by the presence of the characteristic triad of segmental anhidrosis, depressed deep tendon reflex, 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

Introduction

Ross syndrome is characterized by the presence of the triad of segmental anhidrosis, depressed deep tendon reflexes, and tonic pupils.[1] It is a spectrum disorder with Harlequin and Holmes Adie's syndrome at two ends and Ross syndrome a combination of the two.[2] First described in 1958 by Alexander Ross, it is a complex, progressive, degenerative disorder of the peripheral autonomic nervous system of unknown pathogenesis.[1] It is a rare, misdiagnosed autonomic disorder with less than 80 cases reported in the world literature and 24 cases from India.[1-11] Two representative cases of Ross syndrome are presented with their clinical and laboratory correlates and relevant review of literature.

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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 body parts. No motor, somatosensory, bladder, bowel, or visual complaints were noted. Neither history of dizziness, orthostatic hypotension or loss of consciousness nor prior trauma, fever, joint pain, rashes, weight loss, or stroke were noted. Blood pressure was normal without postural drop. Right pupil was midsize with poor reaction to light though preserved to accommodation suggesting unilateral Holmes–Adie pupil [Figure 1]. Skin had variegated color with temperature difference between upper limbs and trunk on either side. There was hyperpigmentation in areas of hyperhidrosis and hypopigmentation over regions with decreased

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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].

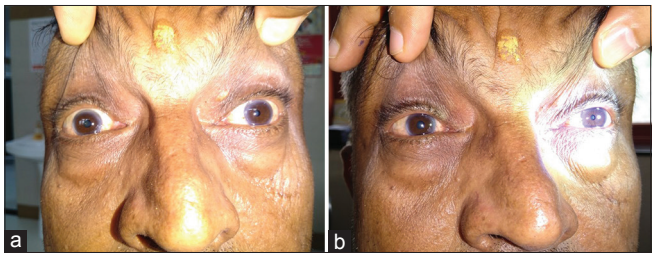

Figure 1: (a and b) Holmes Adie pupil on right side in Case 1

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

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

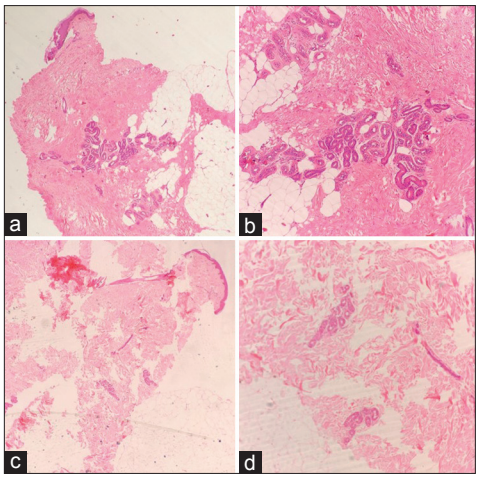

Figure 3: Haematoxylin and Eosin stain of skin in Case 1 (a) at 10× magnification shows focal flattening of rete ridges in epidermis and relative increase in eccrine glands at dermis and subcutaneous junctionfrom left leg; (b) same at 40× magnification; (c) mild acanthosis in epidermis and relative decrease in eccrine glands at lower dermis from right chest at 10× magnification and (d) same at 40× magnification

may result from damage to postganglionic cholinergic fibers to iris and ciliary ganglion leading to cholinergic supersensitivity.[2] Though initially unilateral as in Case 1, it becomes bilateral over years. Other symptoms include orthostatic hypotension, headache, diarrhea, reflux esophagitis, irritable colon, psychiatric disorders, and vasovagal syncope, though a recent study on cardiac and muscle sympathetic nerve activity showed sparing of cardiovascular autonomic system.[4] Both cases reported here demonstrated a similar asymmetrical segmental distribution of sudomotor and skin discoloration involving one half of face, upper limb and trunk, and contralateral lower limb not reported previously. This may suggest dysautonomia at the level of the lower brainstem and upper cervical cord autonomic outflow tracts.

The rarity of Ross syndrome is illustrated by delays in diagnosis and evaluation on part of doctors as well as patients' lack of insight up to 1–13 years (mean 6 years) in a study by Mishra *et al.*[5] Other conditions such as diabetes, leprosy, multisystem atrophy, and congenital insensitivity to pain with anhidrosis or partial anhidrosis (hereditary sensory and autonomic neuropathy type 4 and 5) may cause similar sudomotor symptoms leading to inadvertent delays and need to be recognized by treating family physicians. Tonic pupil that was noted in Case 1 may be seen in diabetes, sarcoidosis, infections, syphilis, and Guillain-Barre syndrome. Etiologically, Ross syndrome may be linked to various factors including viral infections, developmental and genetic factors, and autoimmunity.[6-9] A few reports suggested the role of autoimmune causation.[7,8] Both cases reported did not reveal underlying autoimmunity.

The treatment of this unpredictable disorder is very important though largely unsatisfactory because compensatory hyperhidrosis may lead to heat exhaustion and heat stroke. Systemic anticholinergic drugs (propantheline bromide, glycopyrrolate, oxybutynin, and benztropine) and anxiolytics (beta blockers, amitrypytiline, and fluoxetine) are tried though anticholinergic adverse effects may limit their use. Topical medications (0.5% glycopyrrolate aqueous cream) and local instillation of botulinum toxin may be tried. Modified iontophoretic devices and thoracic sympathectomy for hyperhidrosis have been tried. Steroids are indicated if autoimmune etiology is evident. However, environmental modification, wearing wet clothes during physical activity, and other coping strategies remain the mainstay.

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.

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Conflicts of interest

There are no conflicts of interest.

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