ORIGINAL ARTICLE

Is Ross Syndrome an Autoimmune Entity? A Case Series of 11 Patients

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ABSTRACT: ***Background:*** Ross syndrome is diagnosed by the presence of segmental anhidrosis, areflexia, and tonic pupils. Fewer than 60 cases have been described in literature so far. There have been reports of presence of antibodies in such patients, suggesting an autoimmune pathogenesis. ***Methods:*** We describe the clinical profile in this case series of 11 patients with Ross syndrome and discuss the current status of autoimmunity in its pathogenesis and the management. ***Results:*** Of the 11 patients with Ross syndrome there was an almost equal sex distribution (male:female ratio was 1.17:1) and the mean age of onset of symptoms was 26 years. Patients took an average of 6 years to present to a tertiary center. Sixty-three percent of the patients presented with complaints of excessive sweating, whereas only 27% had complaints of decreased sweating over a particular area of the body. Only 45% of the patients had the complete triad of Ross syndrome, which included segmental anhidrosis, tonic pupil, and absent reflexes. Eighty-nine percent of the patients had documented absent sympathetic skin response on electromyography. The various markers of autoimmunity were negative in all patients who were investigated for the same in this series. Ninety percent of the patients were managed conservatively. ***Conclusions:*** These findings suggest that, in Ross syndrome, generalized injury to ganglion cells or their projections are not purely autoimmune-mediated.

RÉSUMÉ: Le syndrome de Ross est-il une affection auto-immune ? Une étude de série de cas chez 11 patients. ***Contexte:*** Le syndrome de Ross est diagnostiqué par la présence d'anhidrose segmentaire, d'aréflexie et d'anomalies de la fonction pupillaire (pupilles toniques). Moins de 60 cas ont été décrits jusqu'à maintenant dans la littérature scientifique. La présence d'anticorps a été signalée chez ces patients, ce qui suggère une pathogénèse auto-immune. ***Méthodes:*** Nous entendons décrire le profil clinique de 11 patients atteints du syndrome de Ross et aborder le thème de l'auto-immunité en ce qui a trait à sa pathogénèse et à la gestion thérapeutique procurée. ***Résultats:*** Sur 11 patients atteints du syndrome de Ross, hommes et femmes étaient répartis dans des proportions presque égales (rapport hommes-femmes de 1,17 à 1). L'âge moyen de l'apparition des premiers symptômes était de 26 ans. En moyenne, les patients ont attendu 6 ans avant de se présenter à un centre de soins tertiaires. Près de 63 % d'entre eux ont fait état d'une transpiration excessive tandis que seulement 27 % ont rapporté une transpiration insuffisante affectant une région particulière de leur corps. Fait à noter, seulement 45% des patients ont dit ressentir la triade de symptômes associés au syndrome de Ross, ce qui inclut l'anhidrose segmentaire, une anomalie de la fonction pupillaire (pupille tonique) et une absence de réflexes. De plus, 89 % des patients ont rapporté une absence de réponse cutanée sympathique au moment d'une électromyographie. Les différents marqueurs spécifiques à l'auto-immunité se sont révélés négatifs chez tous les patients de cette série ayant fait l'objet d'un examen pour les mêmes motifs. Enfin, 90 % des patients ont été traités au moyen de mesures thérapeutiques moins lourdes et non invasives. ***Conclusions:*** Dans le cas du syndrome de Ross, ces résultats nous portent à croire que des dommages généralisés aux cellules ganglionnaires ou à leurs projections ne sont pas uniquement d'origine auto-immunitaire.

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Ross syndrome is diagnosed by the presence of the characteristic triad of segmental anhidrosis, depressed deep tendon reflex, and tonic pupils. Even though this entity was described by Ross more than 50 years ago (in 1958), to date fewer than 60 cases have been reported in literature.[1] It has been postulated that Holmes-Adie syndrome, Harlequin syndrome, and Ross syndrome are different expressions of the same disease.[2] Selective loss of cholinergic sudomotor fibers have been postulated to be the cause of anhidrosis.[3] Involvement of postganglionic cholinergic fibers projecting to the iris results in tonic pupil.[4] The reason for depressed tendon reflexes is unknown. Although the etiopathogenesis of Ross syndrome is not yet known, there have been recent reports of presence of antinuclear antibodies (ANAs) in such patients, suggesting the possibility of an autoimmune mechanism in initiating the disease process.[4] In our study, we assessed the basic autoimmune antibody profile of 11 subjects with Ross syndrome. We also looked at the various treatment strategies used for their management.

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Table 1: Baseline Parameters of All Patients

Number	Age/ sex	Age at onset	Years to diagnosis	Clinical triad Segmental anhidrosis (1) Tonic pupil (2) Areflexia (3)	Ross subtype Complete (1) Incomplete (2)	SSA/ SSB	ANA	SSR	Biopsy Abnormal (1) Normal (2)
1	40/F	35	5	1, 3	2	Neg	Neg	Absent	1
2	41/M	33	8	1-3	1	-	Neg	Absent	1
3	36/F	29	7	1-3	1	-	Neg	Absent	2
4	33/F	28	5	1-3	1	Neg	Neg	Absent	1
5	41/M	31	10	1-3	1	Neg	Neg	Absent	2
6	45/F	42	3	1, 3	2	Neg	Neg	Absent	-
7	19/M	18	1	1, 3	2	Neg	Neg	Present	1
8	25/F	22	3	1, 3	2	Neg	Neg	Absent	-
9	41/M	38	3	1, 3	2	Neg	-	-	-
10	22/M	22	13	1-3	1	-	-	Absent	-
11	30/M	23	7	1-3	1	Neg	Neg	-	-

ANA, antinuclear antibody; F, female; M, male; neg, negative; SSA/SSB, anti-Sjögren syndrome–related antigen A/B.

Methods

We included all patients diagnosed with Ross syndrome between April 2004 and July 2015 in this case series. The details were obtained retrospectively from outpatient medical records database of our institution, Christian Medical College Vellore, a tertiary health care center in South India. Details of demography, clinical profile, and laboratory and electrophysiological findings were analyzed. A comprehensive autoimmune workup included assessment of ANAs and anti-Sjögren syndrome–related antigens A and B (anti-SSA, anti-SSB) levels. Microsoft excel version 2010 was used to enter and analyze descriptive data.

Results

The clinical features of the 11 patients are described in Table 1. Incidence of Ross syndrome was equal in both males (n = 6, 54%) and females (n = 5, 46%). Mean age of presentation for women was 31 years (22-42) and for men was 27 years (18-38). The mean duration of time delay from the onset of symptoms to diagnosis of the disease was 6 years (1-13). In all patients, this clinical entity was suspected and diagnosed in a tertiary care center. The most common presenting complaint was hyperhidrosis and was present in 63% (n = 7) of patients, which was followed by hypohidrosis and heat intolerance, which were present in two patients each (18%). Although six patients (54%) had clinical features of segmental anhidrosis, tonic pupils, and areflexia establishing the diagnosis of complete Ross, five (46%) had only two components of the triad, suggestive of an incomplete Ross syndrome. All patients with incomplete Ross syndrome had segmental anhidrosis along with areflexia. Three of these patients also had overlying hyperpigmentation of the skin. One patient who presented 13 years after onset of symptoms had significant postural hypotension at the time of presentation. Yet another patient had complaints of blurred vision.

Patients presenting with the complete triad had an average time to diagnosis of 8.3 years since onset of illness compared with only 3 years among patients with incomplete presentation. Electrophysiological studies were done in 9 of the 11 patients, among which sympathetic skin response (SSR) was absent in 78% (n = 7) patients. In the two patients with normal response, SSR was elicited from bilateral palms and soles but not from the areas of anhidrotic patches. Skin biopsy was performed on six patients, among whom four had decreased sweat gland complexes over the anhidrotic areas and preserved sweat gland complexes over the hyperhidrotic region. In two patients, the skin biopsies were normal; however, a repeat biopsy was not done. These patients did not have any other comorbid illnesses. To evaluate for a possible autoimmune etiology, these patients had undergone a panel of tests for autoimmune markers. However, ANAs (9/11], anti-SSA (8/11), and anti-SSB (8/11) were negative in all those who underwent the testing. These subgroups of patients were negative for HIV, hepatitis B virus, hepatitis C virus, and Venereal Disease Research Laboratory test. Magnetic resonance imaging of the spine was normal in all patients. Management strategies were limited. All patients were educated regarding the nature of underlying condition. Ninety-one percent (n = 10) of all the patients were managed conservatively with instructions regarding symptoms control. These patients were advised regarding wearing wet clothing during physical activity to prevent hyperthermia and avoiding heavy work in a hot environment. Botulinum injection and topical glycopyrrolate were administered in only one patient each.

Discussion

Ross syndrome is a rare autonomic disorder of sweating. This syndrome includes the characteristic triad of tonic pupils, areflexia, and segmental hypohidrosis as described initially by Alexander Ross.[5] This benign, progressive autonomic dysfunction has been known to have a slight male preponderance with no specific ethnic predisposition.[5] The disease has been known to occur in any age group and is diagnosed more often in patients in their third decade of life.[5]

Hypohidrosis in Ross syndrome is segmental and progressive. This is secondary to damage to postganglionic sympathetic fibers innervating the sweat glands. Microneurographic studies have

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confirmed the selective involvement of skin sympathetic activity with spared muscle sympathetic activity.[6,7] Most patients also complain of compensatory hyperhidrosis and heat intolerance. This hyperhidrosis is attributed to early loss of cholinergic M2 inhibitor presynaptic autoreceptors. Thermoregulatory impairment is the result of a complex disorder of cutaneous innervation that involves cholinergic sudomotor damage with involvement of pilomotor and vasomotor fibres and to a lesser extent of somatic unmyelinated and myelinated nerve fibers.[1] Anhidrosis may be associated with other features suggestive of autonomic dysfunction, such as cardiac dysautonomia and postural hypotension.

Pupils in Adie's or Ross syndrome are described as tonic, dilated pupils with diminished light reflex. In Ross syndrome, pupillary involvement can be unilateral, which can gradually progress over the years to become bilateral. Clinically, this can present as anisocoria at the onset of the disease. Ten percent of these patients can have a nonresponsive sphincter pupillae and most will have some residual light reflex on examination.[6] The aberrant regeneration of nerve fibers following damage to parasympathetic cholinergic fibers between iris and ciliary ganglion leads to progressive miosis in these patients.[5,6,8]

The reason for the lost or diminished deep tendon reflexes seen in patients with Ross syndrome remains unknown. The damage of the dorsal root ganglia or the spinal interneuron loss has several postulated causes. Because both the peripheral autonomic nervous system and the dorsal root ganglia develop from the neural crest cells, it is possible that they are prone to similar injuries.[2,9] Diagnosis of complete Ross syndrome is clinical and requires the presence of the typical triad. In the absence of the typical triad, a diagnosis of incomplete Ross syndrome is made. Previously reported incomplete Ross syndromes had preserved reflexes even after a follow-up of 9 years.[10] Nevertheless, in the literature, there are reports of incomplete Ross syndrome in the absence of Adie's pupil and areflexia.[11] Among our patients, six (55%) had complete Ross and five (45%) had incomplete Ross syndromes. A noteworthy finding is that none of the patients with a diagnosis of incomplete Ross syndrome in our series had Adie's pupil. This has been noted by others.[12]

Initially, the etiology of Ross syndrome was thought to be an unknown injury to the peripheral autonomic system;[13] however, of late, various etiopathogenic processes have been postulated, mostly based on anecdotal case reports. Nagane et al described the first association of Ross syndrome with an infectious agent, namely cytomegalovirus. Although the diagnosis of cytomegalovirus was nondisputable in the given clinical case, the absence of appropriate details on the onset, duration, and progress of each of the patient's symptoms limits the clinician from diagnosing Ross syndrome in an acute setting (9 days for this patient) because it is known to have a chronic course. This particular patient's evaluation was negative for ANAs, anti-Ro (SSA), anti-La(SS-B), and an extensive panel of infectious agents.[14] In a recent retrospective study of 29 patients with Ross syndrome the mean time of diagnosis since symptom onset was reported to be 12 years compared with 6 years in our subgroup of patients.[15]

Luong et al described the association of Ross syndrome in a patient with Sjögren syndrome based on presence of SSA and SSB antibody, along with subjective and objective evidence of sicca symptoms. Although this patient had a chronic disease course as expected, only limited information from the etiological evaluations have been published. Presence of antithyroid antibodies was also reported in this patient.[16] Vasudevan et al reported another patient with ANA positivity. This patient did not have any other clinical or laboratory manifestations suggestive of systemic lupus erythematous. When relevance of the ANA positivity in this patient's condition itself is questionable, attributing an autoimmune etiology based on the same might not be accurate.[4] None of our patients had any antibody (ANA, SSA, SSB) positivity or any clinical features suggestive of autoimmune disease. Nolano et al have reported a familial association of this syndrome.[17] Lack of clarity on the etiology could be attributed to the rarity of the disease itself. This is evident because only around 60 cases of Ross syndrome have been reported to date (including a previous case series of 12 and 7 subjects) despite being described by Ross as early as 1958.[1,7]

With the existing knowledge of this disease, symptom control has been the only form of treatment that can be offered to patients with Ross syndrome. Modification of the work environment is the first step in management. Local instillation of botulinum toxin and 0.5% glycopyrrolate aqueous cream has been used to provide symptomatic relief.[18] Glycopyrrolate exerts antagonistic effect on the cholinergic receptors thereby reducing sweat production. Iontophoreisis[19] and thoracic sympathectomy have been used in patients with severe disabling hyperhidrosis with good results.[20]

Even though our case series did not reveal any association of Ross syndrome with autoimmunity, we would be cautious in suggesting conclusively that autoimmunity is not involved in the pathogenesis of the syndrome for the following reasons: (1) this series included a rather smaller number of cases; (2) patients underwent the screening for autoimmunity only once, at the time of presentation; (3) lack of follow-up data; and (4) the retrospective nature of the study. Because the study was a retrospective one, the details of SSR, extensive autoimmune profile, skin biopsy with cholinergic innervation of sudomotor fiber, and morphometric analysis of sweat glands were not available in all the patients.

A future step to better understanding the disease would be a common data base of patients with Ross syndrome. This, along with the availability of dedicated clinicians, researchers, societies, and funding allocations, would go a long way in establishing protocols for diagnosis, etiological workup, severity assessment, management, and follow-up. Until that time, an approach based on consensus would facilitate uniformity in the management of Ross syndrome around the world.

Conclusions

Ross syndrome is a rare disease of young onset and can affect both sexes equally. Although a cardinal characteristic of the disease is anhidrosis, the majority of patients can present with complaints of hyperhidrosis. In patients presenting with hyperhidrosis, other components of Ross syndrome should be looked for. The complete triad can be seen in patients with a longer duration of the illness. Among the various etiopathogenesis postulated, autoimmune mechanism is rather unlikely. Conservative management has been the mainstay of therapy; however, a longer follow-up of these patients is required for better understanding risk factors, pathogenesis, and management.

Disclosures

None.

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Statement of Authorship

AKM and MK undertook the study concept and design. AKM, MK, DP, and VM undertook acquisition of data. AKM and MK undertook statistical analysis. AKM, AAG, and CKK undertook data interpretation. AKM, AAG, CKK, and RABC undertook critical revision of the manuscript for important intellectual content. DP, VM, and SGH supervised the study.

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