Commentary

Although first described by Mosier *et al.* in 1953,^[1] the eponym is due to the Ross' report published five years later.^[2] Since these descriptions, less than one hundred cases have been reported in the literature. Most of them as isolated cases, although there are some small series.

The triad segmental anhidrosis/hypohidrosis, Adie's pupil, and hyporeflexia define this syndrome; however, the complete syndrome may need many years to be established. Thus, incomplete forms of Ross syndrome are rather common. In addition to the triad, other clinical findings such as ortostatic hypotension, diarrhea, or cough are occasionally reported. Sometimes, more complex pictures are reported. In this issue, we can find a nice case of Ross syndrome associated with cough and Horner syndrome.^[3] In spite of the complexity of the case, curiously, as the most of the patients, the major complaint was hyperhidrosis.

There are many difficulties in the study of patients with Ross syndrome. One of them is the natural history of the disease as signs and symptoms evolve through years. For example, Adie's pupil is initially a midriatic pupil that neither reacts to light nor accommodation; with time, only alteration to light reflex persists and finally, the pupil loss the midriatic aspect to show even a miotic pupil. About anhidrosis, the intradermal injection of pilocarpine 0.1% or methacoline 0.1% is useful to determinate the location of the alteration in the neural via. Thus, if the injection provokes sweating, it indicates a preganglionic lesion. Unfortunately, this reflex is lost after two years.

Another problem is the lack of consensus about how to study the hyperhidrosis/hypohidrosis. The starch iodine test is widely used for sweating study. Nevertheless, this

is a qualitative test that differentiate two areas of different sweating rate, but it can't determinate what the altered area is. Furthermore, the way to get sweating is variable; some authors use a cabin where the temperature and the humidity are controlled, while others get the sweating after physical exercise or by intaking hot drinks. Some authors report a compensatory hyperhidrosis in Ross syndrome, but is it a real compensatory hyperhidrosis or is it a misperception of the patients? Most of patients situate the hyperhidrotic zone in the opposite area of hypohidrosis; so, it is easy to feel the hypohidrotic area as the normal area. A quantitative test such as QSART (quantitative sudomotor axon reflex test) could resolve this problem. Nevertheless, this test has important limitations. We cannot draw a sweating map with QSART, the reference values are not uniformly determined, and it is only available in few laboratories.

The pathogenic mechanism is still obscure. There is no mechanism that can convincingly explain all the changes in Ross syndrome. The selective loss of cholinergic sudomotor fibers demonstrated by immunohistochemical study of skin biopsies with the panneuronal marker protein gene product 9.5 (PGP 9.5) and the vasoactive intestinal peptid (VIP) as marker of cholinergic fibers was pointed as the cause of anhidrosis in Ross syndrome.^[4] This could explain the progression of the hypohidrotic area, but why is segmental this hypohidrotic zone, and why do this area never cross the midline? A more central lesion could atrophy the sudomotor fibers with time, in this way explaining the immunochemical findings and the distribution of the hypohidrotic areas; however, it would be difficult to explain that only sweating, and sometimes vascular reactivity, was involved.

A degenerative theory has been suggested, but there are no findings that support this hypothesis. Some reports suggest that Ross syndrome could be an autoimmune disease on basis of the positivity of ANA,^[5] or association with Sjögren syndrome.^[6] Although in Ross syndrome both systems sympathetic and parasympathetic are involved; the acetylcholine is the neurotransmitter in both the sudomotor fibers and the neural fibers of pupil. With this common point, one can speculate that an anti-acetylcholine antibody could be pathogenically important. However, at least one report has failed to demonstrate the presence of ganglionic acetylcholine receptor antibodies.^[6] On the other hand, this antibody

seems to be the marker of the autoimmune autonomic ganglionopathy, a disease with few overlap with Ross syndrome.^[7] Finally, a sole report convincingly attributes Ross syndrome to a cytomegalovirus infection.^[8]

To advance in the knowledge of this intriguing syndrome, we have to develop appropriate and validate tests and try to determine the pathogenic mechanism of this rare entity.

Enric Pique-Duran

Department of Dermatology, José Molina Orosa Hospital, Arrecife de Lanzarote, Las Palmas, Spain

Address for correspondence:

Dr. Enric Pique-Duran,
Department of Dermatology, José Molina Orosa Hospital,
Ctra Arrecife-Tinajo,
KM 1,3, Arrecife - 35500, Las Palmas, Spain.
E-mail: epiqued@medynet.com

References

1. Morsier G, Franceschetti A. Two cases of Weill-Reys-Adie syndrome. One of them with migraine and thyroid alterations, and the other with narcolepsy and hemianhidrosis fascio-brachial. *Rev Oto -Neuro -Ophthalmol* 1953;25:5-11.
2. Ross AT. Progressive selective sudomotor denervation; a case with coexisting Adie's syndrome. *Neurology* 1958;8:809-17.
3. Baran A, Balbaba M, Demir CF, Özdemir HH. A case of Ross syndrome presented with Horner and chronic cough. *J Neurosci Rural Pract* 2014;4:394-397.
4. Sommer C, Lindenlaub T, Zillikens D, Toyka KV, Naumann M. Selective loss of cholinergic sudomotor fibers causes anhidrosis in Ross syndrome. *Ann Neurol* 2002;52:247-50.
5. Vasudevan B, Sawhney M, Vishal S. Ross syndrome with ANA positivity: A clue to possible autoimmune origin and treatment with intravenous immunoglobulin. *Indian J Dermatol* 2010;55:274-6.
6. Luong M, Jomir L, Labauge P, Dandurand M, Meunier L, Stoeber PE. Ross syndrome with sweating anomaly associated with Sjögren syndrome: An infrared thermo-graphic case study. *Acta Derm Venereol* 2011;91:80-1.
7. Gibbons CH, Freeman R. Antibody titers predict clinical features of autoimmune autonomic ganglionopathy. *Auton Neurosci* 2009;146:8-12.
8. Nagane Y, Utsugisawa K. Ross syndrome associated with cytomegalovirus infection. *Muscle Nerve* 2008;38:924-6.

Access this article online

Quick Response Code:

Website:

www.ruralneuropractice.com