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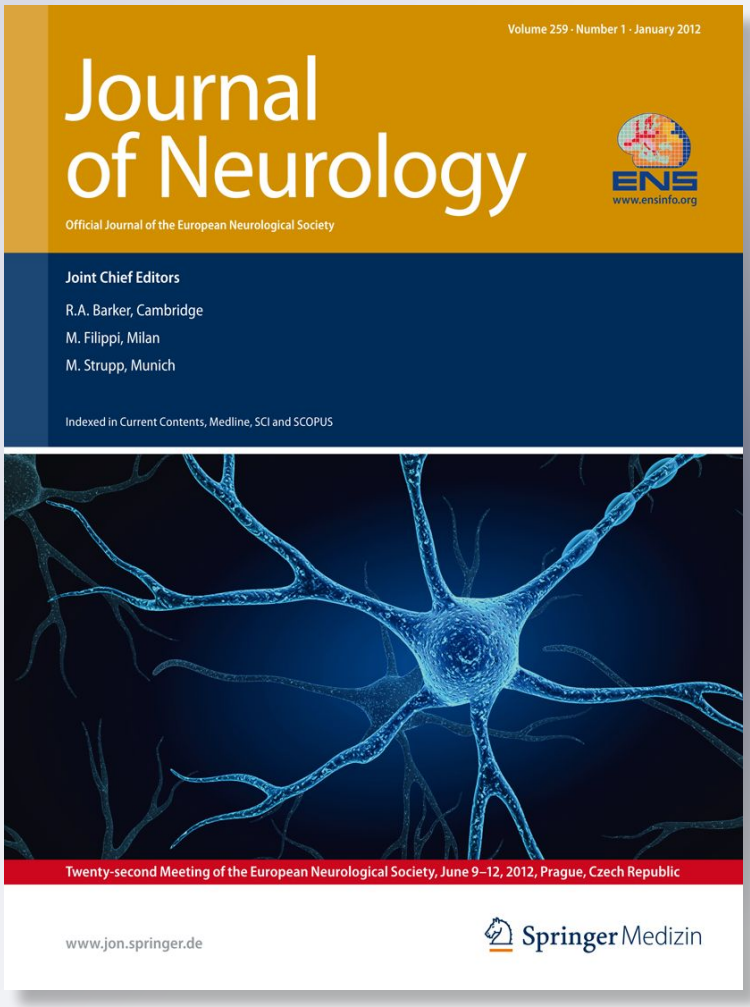
Journal of Neurology
Official Journal of the European Neurological Society

ISSN 0340-5354
Volume 259
Number 4

J Neurol (2012) 259:756-758
DOI 10.1007/s00415-011-6237-0



Springer

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LETTER TO THE EDITORS

Recurrent hypothermia with hyperhidrosis in two siblings: familial Shapiro syndrome variant

Vincenzo Belcastro · Pasquale Striano · Laura Pierguidi · Marco Arnaboldi · Nicola Tambasco

Received: 15 July 2011 / Revised: 28 August 2011 / Accepted: 30 August 2011 / Published online: 17 September 2011

Dear Sir,

A 21-year-old woman was referred for recurrent (up to 2 times per month) episodes of generalized hyperhidrosis and hypothermia with a core temperature fluctuating between 32 and 35°C, lasting from 2–3 h. During these attacks, the woman sweated profusely and felt faint; her skin was pale and cool and sinus bradycardia (<50 bpm) was observed. At admission, blood chemistry and cell count were unremarkable. Ictal EEGs, ECG Holter, and echocardiography were unremarkable. Brain MRI revealed the total absence of the corpus callosum (Fig. 1b). The patient had normal mental status and did not display facial dysmorphisms. No neurologic or physical abnormalities were noted. Endocrine evaluation of hypothalamic-pituitary axis, thyroid, adrenals, and gonads was unremarkable. Electroencephalograms and lack of response to anticonvulsants (levetiracetam 1,000 mg twice/day) excluded the epileptic origin of the attacks.

Her 11-year-old brother suffered from episodes of hypothermia associated with pallor and profuse sweating, lasting for approximately 1 h from the age of 9 years. His axillary body temperature during the episodes was 34.5°C. These episodes recurred up to ten times per month; they occurred randomly and showed a spontaneous recovery. Possible triggering factors were not recognized by parents. On admission, the boy complained of abdominal pain and he was confused and lethargic. Clinical examination during the attack revealed hypothermia with rectal temperatures as low as 31°C.

No neurologic or physical abnormalities, including facial dysmorphisms, were noted. Blood chemistry and cell count were unremarkable. Morning cortisol, prolactin, growth hormone, LH, and FSH were also normal. EEG and brain MRI were normal (Fig. 1a). The diagnosis of Shapiro' syndrome (SS) was, thus, advanced [1]. Based upon previous cases with similar clinical signs as our patient, we started treatment with clonidine [2–4] at the beginning dose of 25 mcg every 8 h. The size of each dose was gradually increased up to 5 days to a total dose of 150 mcg of clonidine every 12 h. The combination of clonidine medication and continuous intravenous fluids reduced the frequency of attacks during the hospital stay. After 7 days, clonidine treatment was gradually discontinued, tapering over a week. Hypotension and/or sedation were not been recognized during the trial with clonidine in this boy (e.g., weight 65 kg). At the present follow-up, the patients complain about sporadic episodes of hyperhidrosis and hypothermia and intravenous fluids are used during prolonged attacks (e.g., >2 h).

First described in 1969, SS consists of the triad of spontaneous periodic hypothermia, hyperhidrosis, and agenesis of the corpus callosum (ACC) [1]. This clinical picture can occur at any age and about 50 cases have been reported [1–9]. As originally reported by Shapiro et al. [1], the syndrome has ACC as a hallmark. 1 Since then, at least 3 patients have been described without this anomaly and are generally considered to be a variant of the condition [5, 6, 8]. In our cases, although corpus callosum agenesis

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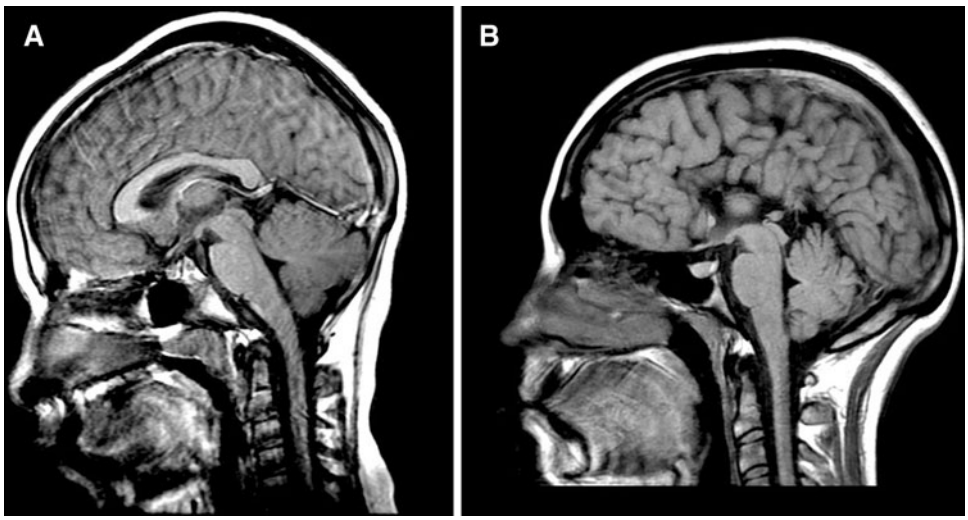

Fig. 1 Sagittal T1-weighted MRIs show a normal view of the brain in the 11-year old boy (**a**) and agenesis of the corpus callosum in his 21-year-old sister (**b**)

was observed only in one sibling, the symptoms of the male patient clearly support the same clinical diagnosis of his sister. Interestingly, recurrent hypothermia has been reported in patients with normal corpus callosum [10]. In this sense, our observations support the view that ACC does not appear to be the cause of SS [5], as persons with isolated ACC may have no symptoms [11]. On the other hand, clinical phenotypes are commonly similar in siblings of a given family, but a greater heterogeneity exists for MRI corpus callosum findings [11]. Noteworthy, SS is a rare presentation of ACC but surgical division of the corpus callosum has not resulted in episodic hyperhidrosis and hypothermia [2].

Hypothermia is another hallmark of SS [1], this cardinal clinical feature has been observed in our and previous cases [1–10]. No single area in the brain is known to control temperature. In fact, thermoregulation involves a complex system of neural connections between the hypothalamus, limbic system, brainstem, spinal cord, and sympathetic ganglia. The primary pathophysiology underlying this disorder is not yet clear but structural or biochemical abnormalities, e.g., basal forebrain malformations or the dopaminergic denervation of the hypothalamic thermoregulatory center, have been suggested [6–9]. Although episodic hyperhidrosis and hypothermia without ACC may be symptomatic of an acquired structural or vascular lesion in the corpus callosum or hypothalamus, neither of the two cardinal features alone is pathognomonic [2].

No definitive treatment for this disorder has been reported and various therapies for recurrent hypothermia have been tried with varying results [4, 5, 8]. Clonidine has been described to help in remission of symptoms in previous reports [2–4] and is proposed to act by regulating the hypothalamic dysfunction [2]. Our patient was treated with 150 mcg of clonidine every 12 h and vigorous intravenous fluids that gave an excellent response with regard to the body temperature. Although we are aware that 150 mcg of clonidine in an 11-year-old child is a large dose, no serious side-effects occurred in our case. Unlike the brother, the sister was not treated with clonidine because of the episodes of hypothermia and hyperhidrosis were not associated with lethargy and confusion.

Shapiro's syndrome has been reported to present sporadically in either sex from age 6 months [12] to 66 years [10], to our knowledge this is the first report of a familial SS variant. These cases expand the spectrum of this rare condition and the occurrence of the disease in two siblings support an autosomal recessive pattern of inheritance. Homozygosity mapping and haplotype sharing analysis in this family may help to identify the causative gene of SS.

Conflict of interest None.

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