

Correspondence

Cold-induced hyperhidrosis: possible association with hyper-IgE syndrome

Cold-induced hyperhidrosis (CIH) is classified into the cold-induced sweating syndrome (CISS) and the acquired idiopathic CIH. Although few mechanistic details are obvious so far concerning both diseases, CISS is documented to include the following phenotypes: (1) congenital anomaly (low set ears, kyphoscoliosis, and hand deformation); (2) upper body sweating triggered by cold temperature, coupled with a paradoxical failure of thermal sweating; and (3) possible relationship with abnormalities of intracellular signaling by ciliary neurotrophic factor (CNTF) receptor.^{1,2}

In the present study, we report a case of CIH in a male patient, with a sweating condition similar to CISS, who had previously also been diagnosed as having hyper-IgE syndrome due to a STAT3 mutation.

An 18-year-old man, who had already been diagnosed as having hyper-IgE syndrome type I (by a STAT3 mutation), was referred to our outpatient clinic for the discomfort due to excessive sweating. Beginning in childhood, his sweating had been excessive on both forearms in cold environments, and this symptom had begun worsening 2 years ago.

He was admitted to our inpatient clinic, and several examinations were performed, including those to evaluate his sweating condition. A physical examination revealed the excrescence of his forehead and lower jaw and the malalignment of his dentition. These features were the typical phenotype of hyper-IgE syndrome with STAT3 mutation (type I). Neurologically, he displayed normal

function of his cranial, peripheral motor, and sensory nerves. Neither orthostatic hypotension nor dysuria was observed. Although the IgE antibody titer was high in his blood test (9697 IU/ml, normal; <173 IU/ml), almost all other parameters – including thyroid functions and autoantibodies – were within normal limits.

Next, we performed a sweating examination by using the iodine–starch method (Minor's sweat test). Hypohidrosis was observed on his upper extremities by the thermal sweating test. For a cold situation-induced sweating test, his lower extremities were immersed into ice-cold water. As expected, perspiration was observed only on his upper extremities and the dorsa of his hands (Fig. 1a–d). Neither pain nor urticaria appeared during the cold stimulus. A quantitative axon reflex sweating test showed reduced sweating on his forearms. Histological analysis of the skin specimens taken from his forearms revealed no abnormalities of his sweat glands.

Because his CIH was not that uncomfortable for him, no special treatment was adopted.

The hypothesized mechanism for cold-induced sweating in CISS is that the disease is a neurological disorder of the sweat glands, as summarized below. Basically, the postganglionic sympathetic neurons innervating the sweat glands acquire a cholinergic phenotype. During embryogenesis, the postganglionic sympathetic neurons express a noradrenergic transmitter phenotype. Usually, gp130-mediated signaling promotes cholinergic neuron differentiation and downregulation of noradrenergic neuron development after birth. The mature eccrine sweat glands are therefore normally innervated by cholinergic

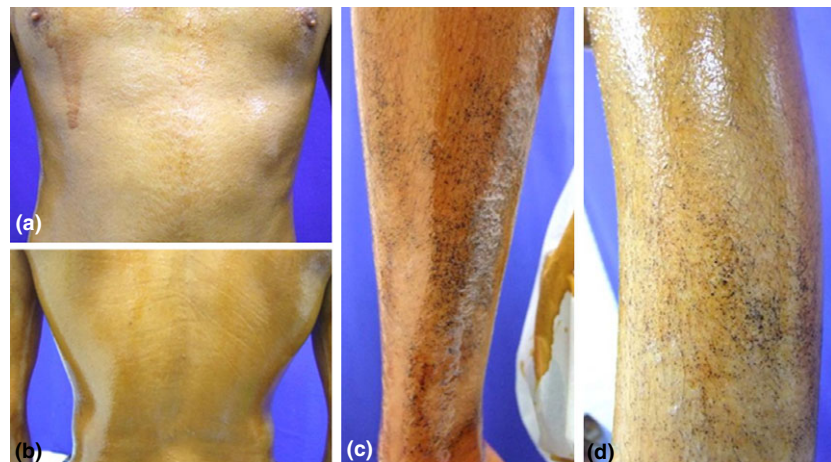


Figure 1 Results of the cold-induced sweating test. The patient's sweating condition was evaluated by the Minor method. (a,b) No sweating was observed on his upper body. (c,d) Sweating was observed on his upper extremities

postganglionic sympathetic neurons. Because the CNTF receptor-mediated signaling pathway, including gp130, is downregulated in CISS, differentiation into a cholinergic neuron is incomplete. Thus, vasoconstriction and perspiration appear due to adrenergic sympathetic activation in a cold environment.³

From the results of his sweating examination (i.e., hyperhidrosis in a cold stimulation-induced sweating test and hypohidrosis in a thermal sweating test were observed on his upper extremities), we considered that his sweating condition resembled CISS. Interestingly, the STAT3 pathway is downstream of intracellular signaling by the CNTF receptor (and gp130). In our CIH case, a STAT3 mutation has already been confirmed because of his hyper-IgE syndrome. These observations suggest to us that an abnormality of the STAT3 signaling pathway other than through a mutation of the CNTF receptor-related proteins may also be involved in the pathogenesis of CISS, although there are no publications that have mentioned a relationship between STAT3 mutation and CISS so far.

Takichi Munetsugu, MD
Ken Igawa, MD, PhD
Tomoko Fujimoto, MD, PhD
Sayaka Shibama, MD

Aya Nishizawa, MD, PhD
Hiroo Yokozeki, MD, PhD
Department of Dermatology
Tokyo Medical and Dental University
Graduate School of Medicine
Tokyo
Japan
E-mail: k.igawa.derm@tmd.ac.jp

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