Letters to Editor

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Hereditary and Sensory Autonomic Neuropathies

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Dear Editor;

We read with interest two recent papers on Congenital insensitivity to pain with anhidrosis, entitled "Congenital insensitivity to pain and anhydrosis (CIPA) syndrome; a report of 4 cases" by Daneshjou et al[1] and "Congenital insensitivity to pain with anhidrosis (HSAN type IV), extremely rare syndrome that can be easily missed by bone and joint surgeons: a case report" by Ali et al[2]. Although the clinical phenotypes of the cases are compatible with diagnosis of congenital insensitivity to pain with anhidrosis (CIPA), different presentations of the disease and lack of simple diagnostic tests makes CIPA a tricky diagnosis[3]. Thus making definite diagnosis should rest on genetic studies.

Hereditary and Sensory Autonomic Neuropathies (HSAN) could be classified into five known subgroups: HSAN1A (OMIM #162400), inherited as an autosomal dominant trait, due to a mutation in the *SPTLC1* gene (OMIM*605712), on chromosome 9q22.1-22, has an onset in the 2nd to 4th decade of life with slow and progressive distal sensory loss due to the dorsal ganglia degeneration and motor loss, leading to weakness and muscle wasting. The patient may complain of paresthesia, numbness, distal motor loss, and heel ulcers[4]. HSAN2A (OMIM #201300), inherited as an autosomal recessive trait, due to a mutation in the *WNK1* gene (OMIM* 605232), on chromosome 12p13.33, has an onset in infancy and early years of life. No pain, thermal, touch, and pressure sensation is reported. Sensory loss has a pattern of glove and stocking, and the deep tendon reflex (DTR) is depressed in some patients. Skin biopsy shows involvement of large and small nerve fibers[4,5]. HSAN3 (OMIM#223900), also known as familial dysautonomia, or Riley Day syndrome, is inherited as an autosomal recessive trait, due to a mutation in the *IKBKAP* gene (OMIM*603722), on chromosome 9q31, and has an onset in infancy and early years of life. This syndrome presents with little or no sensation to pain and temperature, but normal touch sensation. Other features include recurrent gastrointestinal upsets, little lacrimation, anhidrosis, no sensation of tongue, depressed or no DTR, temperature flactuations, recurrent fractures, osteomyelitis, gait difficulties, Charcot joints, ligamentous laxicity, scoliosis, obvious lack of tong fungiform papillae, and no axon flare[4,6]. HSAN5 (OMIM#608654) is inherited as an autosomal recessive trait, due to a mutation in the *NGFB* gene (OMIM*162030), on chromosome 1p13.

HSAN IV, also known as CIPA (OMIM #256800), is inherited as an autosomal recessive trait, due to mutations in the Neurotrophic Tyrosine Kinase Receptor type 1 (*NTRK1*) gene (OMIM*191315), which is also known as *TRKA*, on chromosome 1q21-22[4]. This gene encodes a receptor protein made of 790-796 amino acids, and is divided into extracellular and intracellular domains by a single membrane domain[7]. The *NTRK1* gene via exons 1-8 encodes Nerve Growth Factor (NGF) that is essential for the neural differentiation of the small sensory and sympathetic neurons from the embryonic state[8]. Loss of function mutations of the gene result in loss of mentioned nerves, and this is the key point in understanding the pathophysiology of CIPA. Although there is complete loss of the unmyelinated nerve fibers, reduced small myelinated fibers, and normal distribution of the

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large nerve fibers is also seen[9]. Skin biopsy could be suggested as a second line confirmatory exam for CIPA.

It should be noted that rule out of the common disorders by the strongest possible evidences should be considered as the first step in diagnosis. Although the clinical manifestations of the presented cases are compatible with CIPA, having a confirmatory paraclinic data is also needed, especially because of lack of suggestive family history and rare prevalence of this syndrome. For definite diagnosis of CIPA, genetic analysis of the *NTRK* gene, as the most powerful confirmatory laboratory test, could be recommended in suspicious cases.

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The Effect of Sulfur Mustard on Victims' Offspring; What Is the Challengeable Issue?

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Dear Editor,

We read with interest the Mirsadraee et al's article entitled "Prevalence of Asthma in Children of Chemical Warfare Victims" in the third issue of 2011 [1].

They skillfully reported an interesting investigation about the effect of Mustard Gas (MG) on the victim's offspring. They demonstrated that the asthma was more common amongst children of MG victims compared to the control group. Also they generalized their findings as "chemical agents may increase the prevalence of asthma in the offspring of chemical warfare victims". But it seems that there are some remarks which should be considered before generalizing the results.

Asthma is one of the most common chronic immune based disorders identified with restrictive pattern in pulmonary function test. There are so many factors which promote asthma in children. Exposure to the cigarette smoke can predispose children for asthma or at least one episode of upper respiratory tract infection[2]. In the mentioned study, the prevalence of parental smoking in group with MG exposure was significantly higher than in the control group; therefore it can disturb the findings.

Also, the children with low socioeconomic situation are predisposed for asthma[3] and because of low physical ability to work and high medication cost, the chemical warfare veterans (CWVs) likely are in low socioeconomic situation. Therefore, the authors should have matched cases for the socioeconomic situation but there is no precise information about it.

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