Acquired Neuromyotonia (Isaacs’ Syndrome): A Case Report with Autonomic Physiologic Studies

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Acquired neuromyotonia (Isaacs’ syndrome) is a rare disorder characterized by hyperexcitability of peripheral motor nerves. The cardinal features consist of myokymia, pseudomyotonia and contracture of hands and feet. The diagnosis of Isaacs’ syndrome is based on the clinical features and classic electromyographic findings. Serum antibodies against Voltage-Gated Potassium Channels (VGKCs) are detected in some cases. The authors report a 17 year-old man presented with difficulty in walking, writing and respiratory discomfort for 7 months. His body weight had decreased from 120 to 70 kilograms during that period. Physical examination was remarkable for profound sweating. Muscles were in a state of contraction, action myotonia without percussion myotonia, myokymia and carpopedal spasm. Electromyography showed classical neuromyotonic and myokymic discharges. The investigations for conditions associated with Isaacs’ syndrome were unrevealing. VGKCs antibody were not performed. Treatment with carbamazepine resulted in substantial improvement of the symptoms within 7 days.

Keywords: Acquired neuromyotonia, Isaacs’ syndrome, Myokymia

Acquired neuromyotonia (Isaacs’ syndrome)(1) is a rare disorder where hyperexcitability of peripheral motor nerves leads to incapacitating muscle twitching, cramps, myokymia, pseudomyotonia (slow muscle relaxation after forceful contraction) and mild weakness(2). The muscle cramp may be prominent and accompanied by excessive sweating and weight loss(3). Most patients are sporadic. This is related to the autoimmune mechanism where the autoantibodies are usually detected against the Voltage-Gated Potassium Channels (VGKCs)(4,5). This syndrome may also be related to other autoimmune diseases such as chronic inflammatory demyelinating polyneuropathy, myasthenia gravis or the presence of antiacetylcholine receptor antibodies(6). The association to hematologic malignancies such as thymoma(7,9), plasmacytoma(10), Hodgkin’s lymphoma(2,11) and bronchogenic carcinoma paraneoplastic syndromes, has been documented(5). Another etiology is non-immunologic mechanism from chemical intoxication include mercury, 2,4-dichlorophenoxyacetic acid, dichlorophenyl dichloroethylene and oxaliplatin. Although Isaacs’ syndrome has distinctive features of excessive sweating and profound weight loss, there are no previous electrophysiologic studies of the autonomic nervous system.

Case Report

A hypersthenic17 year-old Thai man, presented with stiffness of limbs that was more pronounced distally for 7 months. He had stiffness that started in the right hand and resulted in inability to relax his hand voluntarily. The stiffness was painless, and was aggravated by voluntary muscle contraction. This symptom progressed to his left hand in a few weeks. The stiffness had become so severe that he could not write properly. Riding a motorcycle was not possible due to the inability to release the hand-clutch. He could not participate in any athletic activities. Five months prior
to admission, his gait became difficult with a rigid manner. Profound sweating without any palpitation became more prominent and body weight decreased from 120 to 70 kilograms. Defecation and micturation were normal. He substantially became a muscular man. Two months before admission, he had involuntarily continuous contraction of muscles of the arms and thighs. All symptoms persisted day and night, even when sleeping. He had also experienced hoarseness of voice, dysphagia, snoring and dyspnea. His past medical history was unremarkable. There was no history of exposure to toxic substances or medications. There was no familial history of these symptoms.

Physical examination revealed a muscular man with excessive sweating. Vital signs were within normal limit. He was intellectually and emotionally normal. Neurological examination revealed normal cranial nerves but his tongue and jaw were stiff. His posture was also stiff and all muscles were in a state of persistent contraction (Fig. 1). The degree of stiffness was more remarkable in the distal than proximal muscles. The most striking physical findings were myokymia (constant undulating movement of the muscles) especially on his arms and thighs and action myotonia. However, percussion myotonia was absent. Passive movement was painless. He had lateral trunk bending and walked in toe to toe gait. Muscle strength was normal but tone was generally increased. Sensory examination was intact. Deep tendon reflexes were not elicitable due to stiffness and down turned toes. Lymph nodes and thyroid gland were not palpable. Abdominal wall was tense but there was no hepatosplenomegaly or palpable masses. There was no other evidence of systemic diseases.

Complete blood count, erythrocyte sedimentation rate and other blood chemistries including calcium, phosphate and magnesium levels were normal. Lactate DeHydrogenase (LDH) was tested twice and appeared to be mildly elevated, 669 and 518 (normal 230-460). Serum creatine kinase was normal. Computerized tomography of the chest and abdomen showed no mediastinal mass or other abnormalities. Thyroid function tests were normal. Lumbar puncture revealed clear cerebrospinal fluid with only one mononuclear cell, normal protein (24 mg/dL) and sugar (59 mg/dL). CSF oligoclonal band and cytospin were negative.

Conventional physiologic studies were tested and revealed abnormal spontaneous activities particularly myokymic discharges (Fig. 2). Fibrillation, positive sharp waves and continuous muscle fiber activities that fired at frequencies of 100 to 300 Hz (neurotonic discharges, or neuromyotonia) were also presented (Fig. 3). In addition, motor nerve conduction studies showed stimulus-induced repetitive discharges on

Fig. 1 Demonstration of generalized muscle contracture and stiff posture
Isaacs’ syndrome is a rare syndrome that has never been reported in Thailand. This syndrome has been occasionally mentioned in Asian literatures especially in Japan and China(12-15). The diagnosis of Isaacs’ syndrome is based on clinical features and electromyographic findings. The cardinal features consist of myokymia, pseudomyotonia and stiffness of trunk and limbs. Stiffness without severe pain is more pronounced in the distal than proximal muscles. This abnormal activity persists during sleep. Dyspnea may occur when respiratory muscle is involved. There have been only a few reports of bulbar and laryngeal involvement in Isaacs’ syndrome(2). The tongue and jaw become stiff, making swallowing difficult, and the voice turn hoarse(1). Associating symptoms include weight loss and excessive sweating.

Neurological examination in Isaacs’ syndrome reveals myokymia, pseudomyotonia and carpopedal spasms (contracture of hands and feet). All musculature is in a state of continuous contracture, while muscle power is intact. Posture may be abnormal with exaggerated kyphosis and movement is slow. Deep tendon reflexes are usually normal to absent and plantar response is flexor. Systemic examination may show excessive sweating.

Classical electrodiagnostic studies detect myokymic and neuromyotonic discharges. In addition, fasciculation, doublet, triplet, multiplet and positive sharp waves are also demonstrated in this syndrome. Stimulus-induced repetitive discharges, usually seen after the M wave, are also demonstrated during motor nerve conduction studies(16,17).

In the presented patient, his syndrome consisted of myokymia, pseudomyotonia and stiffness of trunk and limbs. Bulbar and laryngeal involvement occurred late in his clinical course. Electrodiagnostic studies were compatible with classical findings of Isaacs’ syndrome. Sudomotor function was tested and revealed normal SSR. This suggested that excessive sweating may be related to the heat generated by excessive muscle activity rather than autonomic system involvement.

Isaacs’ syndrome is a channelopathy that results from an antibody-mediated attack against peripheral nerve VGKCs(4,18). Nevertheless, antibodies against VGKCs were not detected in all patients. Mogyoros et al stated that at least eight different potassium channels were identifiable on myelinated axons(19). Hart et al reported that alpha-dendrotoxin receptor immunoprecipitation assay detected only a subset of potassium channel antibodies(5). Negative antibody tests do not exclude the diagnosis since there are antibodies specific for neuronal potassium.
channels that do not bind to $^{125}$I-alpha-dendrotoxin or the antibodies levels may be too low to be detected(2,18). Other etiologies of acquired neuromyotonia were excluded by appropriate investigations as well as the long term follow up of the clinical course. The elevation of LDH level in this patient may due to a non-specific inflammation or cell damage in generalized muscle hyperactivity(20). Electrophysiological studies, as well as pharmacological, immunologic and therapeutic responses to anticonvulsants indicate that the site of origin of spontaneous discharges is principally in the distal portion of the motor nerve and/or within the terminal arborization(18,21-24).

Autoimmune related Isaacs’ syndrome usually has a benign course. Treatment with antiepileptic drugs or immunotherapy often improves the clinical and electrophysiologic findings. Most patients have remission after treatment for 13 months(8-18months) and can be withdrawn from drugs(9). In nonresponders, immunotherapy with intravenous immunoglobulins, plasmapheresis, and corticosteroids have been tried successfully(12,25,26). The presented patient’s symptoms were substantially improved within 7 days by carbamazepine. After a one year follow up, he could resume his normal activities of daily living and no evidences of systemic autoimmune diseases or malignancies have been observed.

References
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แอคไควนิวโรมัยโอโทเนีย (กลุ่มอาการไอแสค) รายงานผู้ป่วยกับการศึกษาสรีระของระบบประสาทอัตโนมัติ

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แอคไควนิวโรมัยโอโทเนีย (กลุ่มอาการไอแสค) เป็นความผิดปกติที่พบน้อยเนื่องจากมีการกระตุ้นเส้นประสาทมอเตอร์ส่วนปลายมากเกินอาการสำคัญมีมัยโอไคเมีย, มัยโอโทเนียปลอมและการหดเกร็งของมือและเท้า การวินิจฉัยกลุ่มอาการไอแสคอาศัยอาการและการตรวจทางไฟฟ้ากล้ามเนื้อและบางรายอาจตรวจพบแอนติบอดีต่อโวลเตจเกตโพแทสเซียมแชนแนล รายงานนี้แสดงผู้ป่วยชายอายุ 17 ปี มีการเดินลำบาก เขียนหนังสือไม่ถนัด และหายใจไม่อิ่มมา 7 เดือน น้ำหนักต่ำลงจาก 120 เป็น 70 กิโลกรัม การตรวจจงทางพบเชื้อมากมัยโอไคเมีย การทดสอบฝัดกล้ามเนื้อและตรวจหาโรคร่วมต่าง ๆไม่พบความผิดปกติ ไม่สามารถตรวจพบตับต่อโวลเตจเกตโพแทสเซียมแชนแนลได้ อาการของผู้ป่วยดีขึ้นมากภายในเวลา 7 วันหลังได้รับยาคาบามาซีปีน

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