Hoffmann's syndrome: a case report

Hoffmann-Syndrom: ein Fallbericht

Abstract

This syndrome is characterized by the presence of hypothyroidism with myxoedema, muscle stiffness and pseudo hypertrophy. We describe the disorder in a 21 year old male, who got admitted with complaints of generalized weakness, cold intolerance, constipation, and hoarse voice, difficulty in walking and progressive enlargement of muscles of thighs and back with crampy pains for two years. Examination revealed mild mental retardation, enlarged tongue, dry and rough skin, enlargement of thighs and back muscles, motor weakness in flexors of hips and knees with delayed relaxation of deep tendon reflexes. Investigations revealed evidence of hypothyroidism with marked elevation of muscle enzymes. Following institution of replacement therapy with thyroxine, the patient showed marked clinical and biochemical improvements after six months, but insignificant decrease in muscle mass. In this report we review relevant literature.

Keywords: hypothyroidism, myopathy, pseudohypertrophy

Zusammenfassung

Das Syndrom ist charakterisiert durch eine Hypothyreose mit Myxoedem, Pseudohypertrophie und Steifheit der Muskulatur. Das Syndrom wird beschrieben an einem 21-jährigen Patienten, der in die Klinik aufgenommen wurde wegen allgemeiner Schwäche, Kälteunverträglichkeit, Obstipation, Änderung in der Stimmlage, Schwierigkeiten beim Gehen bei gleichzeitiger Verdickung der Muskulatur an den Beinen und im Rücken mit Muskelkrämpfen. Die Beschwerden bestanden seit zwei Jahren. Die klinische Untersuchung ergab eine geringe geistige Retardierung, eine vergrößerte Zunge, trockene und raue Haut, Hypertrophie der Muskulatur an den Oberschenkeln und im Rücken, der Flexoren im Kniegelenk mit verlängerter Relaxation der tiefen Sehnenreflexe. Die Laboruntersuchungen ergaben Hinweise für eine Hypothyreose mit erhöhter Aktivität der Muskelenzyme. Nach Beginn der Substitutionstherapie mit Thyroxin über sechs Monate zeigte der Patient deutlich verbesserte klinische und biochemische Ergebnisse, aber nur einen geringgradigen Rückgang der Muskelmasse. Die einschlägige Literatur wird in diesem Bericht besprochen.

Waseem Qureshi[1]
Ghulam Hassan[2]
Ghulam Qadir Khan[2]
Syed Manzoor Kadri[3]
Manish Kak[2]
Manzoor Ahmad[2]
Shahid Tak[2]
Darshan Lal Kundal[2]
Showkat Hussain[2]
Abdul Rashid Rather[2]
Ibrahim Masoodi[2]
Sabia Sikander[2]

1 SMHS Hospital, Srinagar, Kashmir, India

2 Department of Medicine, Government Medical College, Srinagar, Kashmir, India

3 Regional Institute of Health & Family Welfare (RIHFW), Directorate of Health Services, Srinagar, Kashmir, India

Introduction

Hoffmann's syndrome, first described by Hoffmann in 1897, is characterized by the presence of hypothyroidism with muscle stiffness and pseudo hypertrophy. Whereas muscle hypertrophy with weakness and slowness of movement in cretinous children is known as Kocher Debre Semelaigne syndrome [1], [2], [3], [4], [5], [6], [7], [8], [9], [10]. However the two conditions tend to merge into each other and may even occur, although at different times in the same patient [3].The former in addition is characterized by few other clinical manifestations [6]. This syndrome is a very rare disorder. In India only few cases have been reported so far [2], [7], [8] and to our knowledge the present case is the first case reported from the Jammu and Kashmir State.

Case presentation

A 21-year-old male of non consanguineous parents was admitted to our Department of Medicine, Government Medical College, Srinagar, Kashmir, India with complaints of generalized weakness, cold intolerance, enlargement of muscles of thighs and back and crampy pain in the calf and thigh muscles for the last two years. Further enquiry revealed that he had constipation, hoarseness of voice and difficulty in walking of same duration. His de-

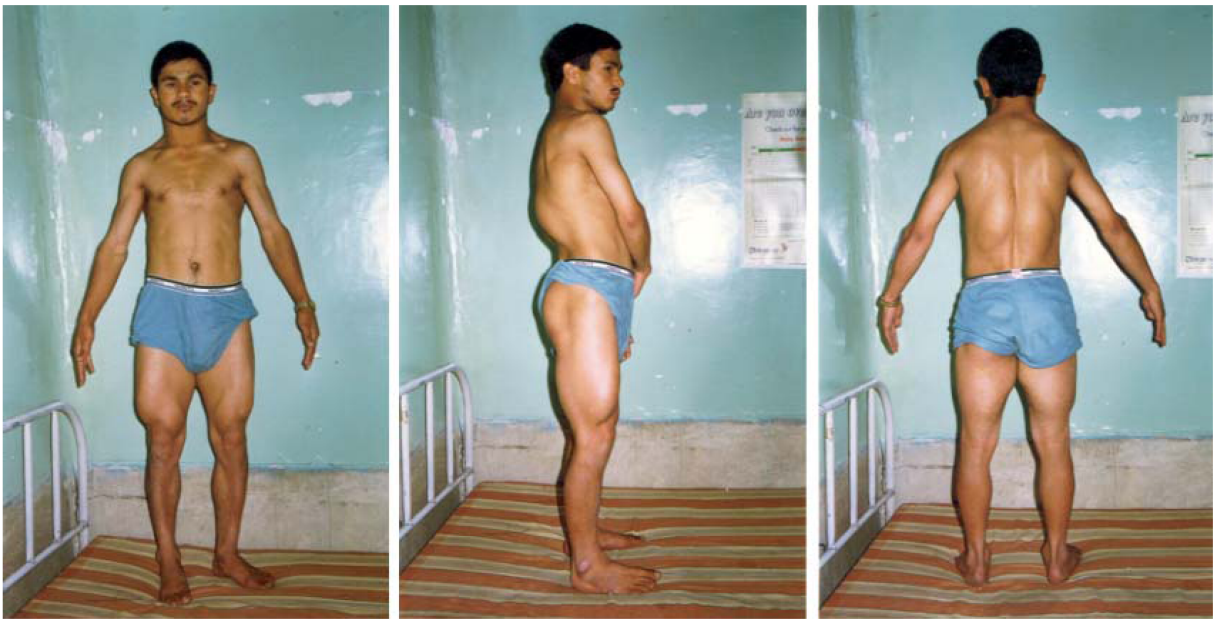

Figure 1: 21-year-old male patient with Hoffmann's syndrome

velopmental history and milestones were consistent with age. There was no history of swelling of or operation on the thyroid gland, any medication prior to the onset of illness or hospitalization for any significant illness in the past. None of the family members from maternal and paternal side suffered from such illness.

On examination he had dull look, mild mental retardation, hoarse voice, moderately enlarged tongue, dry and rough skin and visible enlargement of thigh and back (Figure 1). Thyroid was non-tender and not enlarged, a non-pitting edema was present at the pretibial sites. He appeared lethargic and his activities were slow. Pulse was slow (54 beats/min) regular, without any special character and all the peripheral pulses were palpable and synchronous. Blood pressure was 100/60 mmHg. His body weight was 47 kg, height 151 cm and body mass index (BMI) was 20.6 kg/m^2. Girth at the level of maximum enlargement of muscles of back was 96 cm, that of thigh muscles at the level of maximum enlargement was 49 cm on right and 46 cm on left side. Fundoscopic examination was normal. Genitalia and hair distribution were normal and there was no musculoskeletal deformity. His cardiothoracic and abdominal examination was normal. On neurological examination he was mentally retarded, had grade 4 power of the flexors of hips and knees on both sides, biceps, ankles and knee reflexes had classical delayed relaxation. Investigations on admission revealed elevated serum levels of cholesterol of 320 mg/dl, aspartate aminotransferase (AST) 46 U/L (0-25 U/L), lactate dehydrogenase (LDH) 2432 U/L (100-190 U/L), creatinine phosphokinase (CPK) 763 U/L (25-90 U/L) and aldolase 14.5 U/L (0-6 U/L). Thyroid function testing revealed the serum levels of thyroid stimulating hormone (TSH) elevated to 9.2 µU/ml (0.4-5 µU/ml) and decreased levels of thyroxine (T_4) of 3.2 µg/dl (5-12 µg/dl) and plasma triiodothyronine (T_3) of 43.6 ng/dl (70-190 ng/dl). The electrocardiogram was of low voltage having sinus bradycardia with rate of 52/min. Biopsy of thigh mucles taken at side of enlargement showed hypertrophy of muscle fibers with increased nuclei, few necrotic fibers and mucoid deposits at places and electromyography of hypertrophied muscles revealed complex repetitive discharges. Nerve conduction velocity studies were normal and ultrasonography of thyroid and detailed skeletal survey did not reveal any abnormality. All other hematological, biochemical, serological and endocrinological investigations performed in detail and repeatedly were normal. With the findings of hypothyroidism and muscle hypertrophy, the patient was put on replacement therapy with levothyroxine, started from 25 µg/d and increased to 100µg/d. After this the patient noticed improvement of his symptoms within four weeks. Repeated anthropometric measurements and investigations were performed over a period of six months (Table 1, Table 2). The patient showed marked improvement in symptomatology and biochemical parameters including muscle enzymes but there is no significant improvement of muscle hypertrophy despite months of therapy.

Discussion

The present case got significant improvement of symptoms like cold intolerance, weakness, constipation, hoarseness of voice, muscle cramps, weakness of flexors of hip and knee, pretibial edema, mentation and appearance of skin by three months of institution of thyroxine replacement and the various biochemical parameters returned to normal by 6 months. However, the enlarged muscle mass did not show any significant improvement, although body weight got reduced by 2 kg. The improvement in symptoms and biochemical abnormalities cured in a relatively long period of 3 to 6 months compared to previous studies were the significant improvement was

Table 1: Anthropometric measurements before and after thyroxine replacement

Measurement	Before thyroxine (on admission)	1 month after start of therapy	3 months after start of therapy	6 months after start of therapy
Body weight (kg)	47	47.5	46	45
Height (m)	1.51	1.51	1.51	1.51
BMI (kg/m^2)	20.6	20.8	20.1	19.7
Girth at the level of hypertrophied back muscles (cm)	96.7	96.2	94.5	93.7
Girth at the level of hypertrophied thigh muscles (cm)	49.8 R 46.3 L	49.5 R 46.0 L	48.7 R 46.0 L	47.5 R 45.2 L

R- Right side, L- Left side

Table 2: Laboratory parameters before and after thyroxine replacement

Parameter	Normal value	Before thyroxine (on admission)	1 month after start of therapy	3 months after start of therapy	6 months after start of therapy
Cholesterol (mg/dl)	< 200	320 ↑	286 ↑	189	181
CPK (U/L)	25-90	763 ↑	349 ↑	103 ↑	87
LDH (U/L)	100-190	2432 ↑	843 ↑	311 ↑	176
AST (U/L)	0-35	64 ↑	47 ↑	28	31
Aldolase (U/L)	0-6	14.5 ↑	8.7 ↑	5.9	4.9
TSH (µU/ml)	0.4-5	9.2↑	7.7 ↑	4.1	3.5
T_3 (ng/dl)	70-190	43.6↓	59.8 ↓	171.5	160.0
T_4 (µg/dl)	5-12	3.2 ↓	4.4 ↓	5.6	7.3

observed in shorter period of 10 weeks to 3 months [1], [2], [4], [5], [8]. The insignificant improvement of muscle enlargement in our study is similar to that of Astrom et al. [11] where there was no response to thyroxine therapy for a prolonged period.

Muscular complaints are common symptoms of disorder and increased volume of muscle and slowness of contraction constitute the muscular syndrome [1], [5], [6]. The entire musculature is affected to some extent but the most obvious enlargement is in the tongue, arms and legs. In one woman the biceps had become so thick that she could not touch her thumb and little finger [6]. Chopra et al. [8] noticed hypertrophy of almost all muscles of body, especially calf and arm muscles. In comparison to this we observed enlargement of tongue, thigh and spinal muscles. A sense of stiffness and even slight discomfort in the large muscles are frequent complaints and movements may even be mildly painful. These are probably the expressions of the basic slowness of contraction [3], [5], [6]. Whether this slowness of contraction and relaxation is the same as myotonia, has been a subject of debate. The consensus is that it differs from myotonia and should therefore be called pseudomyotonia. Unlike myotonia there is slowness of contraction and relaxation and slowness of the latter is not increased after rest or relieved by repeated contraction of the muscle. Further striking the muscle belly so called "percussion myotonia" does not elicit a response in pseudomyotonia [6]. Kugelberg (1959) reported 3 cases in whom there was no evidence of myotonia or hypertrophy but those cases proved to have myopathy by electromyographic and histological studies [2]. Muscle biopsies in most of the studies have revealed no abnormalities [1], [4], [6], [8]. The biopsy study in our case showed hypertrophy of muscle fibers with increased nuclei, few necrotic fibers and mucoid deposits at places and the findings are coinciding the studies of Mastropasqua [1] and Mishra [2]

The high level of CPK, LDH, AST and aldolase are indicative of muscle disorder and many studies of skeletal muscle have shown that changes in expression of the myosin heavy gene accompany thyroid states [1], [4]. It is known that hypothyroidism can lead to increase in CPK release from skeletal muscle, serum levels of CPK may be elevated in 70%-90% of hypothyroidism patients. However no correlation has been found between CPK levels and circulating concentration of T_3, T_4 and thyro-

tropin. The presence of triiodothyronine receptor on the mitochondrial membrane of skeletal muscle suggests a direct impact of thyroid hormones on oxidative metabolism and may provide a biochemical basis for the muscle dysfunction in hypothyroidism. Even severe hypothyroidism may reduce glycolysis and oxidative phosphorylation and thus reduce adenosine triphosphate concentrations beyond a critical limit, generating a marked release of CPK through the altered sarcolemmal membrane [1]. Other less common associations of the disorder include peripheral neuropathy, facial weakness, cerebellar ataxia and dementia. Secondary sexual characteristics are not altered [1], [6]. The present case is having no such manifestation and is under our regular follow up for future course.

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Erratum

The name of the co-author Ibrahim Masoodi was first erroneously indicated as Mohammad Ibrahim.

Corresponding author:
Ghulam Qadir Khan
PO Box 1143, GPO, Srinagar 190001, Kashmir, India
kadrism@sancharnet.in

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