HOFFMAN’S SYNDROME

Pseudohypertrophic myopathy as initial manifestation of hypothyroidism

Case report

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ABSTRACT - The frequency of myopathy in hypothyroidism ranges from 30 to 80%. The major symptoms related are weakness, muscular cramps and myalgia. The pseudohypertrophic form is called Hoffman’s syndrome. The electrophysiological study reveals myopathy, neuropathy or mixed pattern. Laboratorial investigation generally shows increased levels of muscle enzymes and low serum thyroid hormones, with thyrotrophic-stimulating hormone (TSH) elevated. The treatment consists in hormone replacement and the prognosis is good in most of the cases. We report an adult male who developed muscular cramps, myalgia, weakness, pseudohypertrophy, associated with facial edema and alteration of his voice. The muscle enzymes were increased and T4 was undetectable with a raised level of TSH. The myopathy was the initial manifestation of hypothyroidism in this case.

KEY WORDS: myopathy, hypothyroidism, pseudohypertrophy.

Síndrome de Hoffman: miopatia pseudohipertrófica como manifestação inicial de hipotireoidismo. Relato de caso

Resumo - A frequência de miopatia no hipotireoidismo varia de 30% a 80%. Os sintomas relacionados ao acometimento muscular são fraqueza, cãimbras e mialgias. A forma pseudo-hipertrófica é denominada síndrome de Hoffman. O estudo eletrofisiológico pode revelar padrão miopático, neuropático ou misto. A investigação laboratorial em geral mostra aumento das enzimas musculares e redução dos níveis de hormônio tireoidiano com TSH elevado. O tratamento consiste na reposição oral de hormônio e o prognóstico é bom na maioria dos casos. Relatamos o caso de um adulto que apresentou cãimbras, mialgia, fraqueza com pseudohipertrofia muscular associados a edema facial e alteração da voz. As enzimas musculares estavam elevadas e o nível de T4 foi indetectável com aumento de TSH. A miopatia foi manifestação inicial de hipotireoidismo neste caso.

PALAVRAS-CHAVE: miopatia, hipotireoidismo, pseudo-hipertrofia.

The thyroid hormone is necessary to cell metabolism of all organic systems. Its deficiency is manifested by a systemic disease with insidious onset. The manifestations on the central nervous system (CNS), are characterized by psychiatric symptoms, cerebellar ataxia, cranial neuropathy and seizures¹. An impairment of peripheral nervous system and muscles leads to different types of neuropathy and myopathy being responsible for 5% of acquired myopathies². The myopathy associated with hypothyroidism could be divided in four subtypes: Kocher-Debré-Semelaigne syndrome, Hoffman’s syndrome, atrophic form and myasthenic syndrome³. In the Kocher-Debré-Semelaigne syndrome described in infants with cretinism, as in the Hoffman syndrome, patients presented with hypertrophy, muscular we-
akness, slowness of mental and locomotor activities. In Hoffman syndrome it is described also muscular cramps, stiffness post-exercise and pseudomyotonic phenomenon. Other less frequent presentations are atrophic myopathy and myasthenic syndrome with unsatisfactory response to edrophonium. In most of the cases, the level of muscular enzymes is elevated, with no relation to the severity of the myopathic symptoms. In primary hypothyroidism, the hormonal dosage shows low circulating of thyroid hormones (T3 and T4) with elevated TSH. Once the hormonal reposition is started, the myopathy could be reversible with good prognosis. Although it is a rare condition, the myopathy may be the first presentation of hypothyroidism.

We present a case in which myopathy was the first symptom of autoimmune thyroiditis.

CASE

A 42 years-old man admitted for diagnostic investigation of progressive muscular weakness with muscular cramps and myalgia started one year before. He had mentioned a gastric surgery for resection of an abdominal tumor (histological diagnostic of non-Hodgkin lymphoma) followed by treatment with chemotherapy nine years ago. Since then, he remained asymptomatic with normal clinical and laboratorial exams. We observed in clinical examination: infiltrated facies, macroglossia and the voice was hoarse cry, hypophonesis of heart sounds and sinus bradycardia (56 bpm). On neurological examination was observed pseudohypertrophy (Fig 1) with proximal paresis of inferior limbs (Grade 4/5 Muscle Research Council [MRC]), generalized hyporeflexia, and superficial hypoesthesia on the distal superior limbs. On the exam of the cranial nerves, bilateral impairment of the cochlear portion of VIII nerve.

Laboratorial investigation reveals (Table 1): (1) increased serum levels of muscular enzymes; (2) mild elevation of serum level of creatinine; (3) leukopenia; (4) dislipidemia degree IV, (5) dosage of thyroid hormones compatible with primary hypothyroidism with raised levels of anti-thyroglobulin (1977 u/ml – Normal: 40 u/ml) and antiperoxidase (>1000 u/ml - Normal: 35 u/ml), (6) electrocardiogram (ECG) showed sinus bradycardia with low voltage in the precordial leads, (7) electrophysiological study showed normal Desmet and repetitive stimulation test. The motor and sensitive neuroconduction did not revealed abnormalities. The first electromyography (February/2001) revealed a diminished recruiting of motor unit (neurogenic pattern). The second exam (April/2001) showed a mixed pattern (myogenic and neurogenic).

After ten days of thyroid hormone therapy, the patient referred improvement of the muscular cramps. Three months latter, he was asymptomatic. There was progressive lowering of the levels of muscular enzymes (Table 1).

DISCUSSION

The neurological manifestations of hypothyroidism usually occur after clinic impairment of other systems, so it is unusual to see it as the initial symptoms. Primary hypothyroidism accounts for 95% of

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<th>Table 1. Laboratorial exams.</th>
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<td>Period</td>
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<tr>
<td>Before treatment</td>
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<td>After treatment φ (1 month after)</td>
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<td>After treatment ϒ (3 months after)</td>
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φ in use of 75 µcg of thyroxine; ϒ in use of 125 µcg of thyroxine; T4, free thyroxine (N 0.71 – 1.85 ng/100mL); TSH, thyrotrophic-stimulating hormone (N 0.47 – 5.01 mU/mL); TG, triglyceride (N 10-170 mg/dL) Cholesterol (N 150 - 250 mg/ dL); CPK, creatinophosphokinase (N 26 - 174 U/L); LDH, lactic dehydrogenase (N 150 360 U/L); AST, aspartate aminotransferase (N 12-46 U/L); VNO, value not obtained.

Fig 1. Before and after treatment showing the resolution of pseudohypertrophy.
raised levels. The fall on the enzyme levels with the
of CPK may vary from low elevations to extremely
level, or the opposite. The alteration of the level
patient may be symptomatic and have a normal CPK
clinical picture in the case of hypothyroidism, the
of hepatopathy. ALT, LDH) have a complementary role in the absence
of myopathies. The other enzymes (aldolase, AST and
phosphokinase (CPK) is the best biochemical marker
of muscular enzymes. The creatinophosphokinase (CPK) is the best biochemical marker
of myopathies. The other enzymes (aldolase, AST and
ALT, LDH) have a complementary role in the absence
of hepatopathy. In a study performed by Gianpietro
et al. to determine the most sensitive enzyme to
investigated myopathy, the CPK was elevated in 60%
cases, in the superior limit in 30% and normal in
10%, showing that this enzyme is the best bio-
chemical marker for the investigation of myopathies,
because it is a low cost method, sensitive and easy
to perform. The level of CPK does not relate to the
clinical picture in the case of hypothyroidism, the
patient may be symptomatic and have a normal CPK
level, or the opposite. The alteration of the level
of CPK may vary from low elevations to extremely
raised levels. The fall on the enzyme levels with the
treatment occurs slowly, varying from weeks, months
or even years. In the presented case, muscular
enzymes returned to normal values in three months.

The electrophysiological study may be compatible
with neurogenic, myogenic, a mix of those patterns,
or even normal. The findings compatible with myo-
genic pattern are diminished duration and amplitude
of motor unit potential, increase in polyphasics,
with voluntary contraction there is early recruiting
of the short action motor units, spontaneous fibril-
lations, positive waves and complex repetitive dis-
charges. Cruz et al. showed, in a study with 16
patients with primary hypothyroidism, electrophys-
iological abnormalities in 87.5% of the patients,
being 46.6% with myopathic pattern, 43.7% with
neuropathic pattern (carpal tunnel syndrome), and
25% with a mixed pattern. The referred patient pre-
vented mixed pattern with carpal tunnel syndrome.
In the case, despite the expressive clinical improve-
ment with normalization of muscular enzymes, some
electroneurophysiological alterations persisted as
early recruiting, polyphasics, and bilateral carpal
tunnel syndrome.

Pseudohypertrophy etiology in Hoffman’s syn-
drome remains obscure and a matter of discussion.
It has been postulated that the mechanisms involved
could include an increase in connective tissue,
increase in the size of muscular fibers and increase
of the number of muscular fibers. Ono et al., in a
study made with cases of hypothyroidism causing
myopathy, showed that the diameter of the type I
and II fibers could be normal and there was not an
increase in the connective tissue, so the hypertrophy
of muscular fibers and increase in connective tissue
may be absent in Hoffman’s syndrome. The severity
of the myopathic picture seems to be related to some
findings of muscular biopsy. In severe cases there is
atrophy of type II muscular fibers, associated to cen-
tral core of the nucleus, mainly of the type II muscu-
lar fiber. On optic microscopy the alterations are
atrophy, necrosis, muscular fibers hypertrophy,
increase in the number of nucleus, ring-shaped
fibers, glycogen deposits and increase of connective
tissue. Ultra-structural analysis showed edema and
mitochondrial inclusions, myofibrillar fragmentation,
glycogen deposits, lipid granule, sarcoplasmatic reti-
culum dilatation, autophagic vacuole, changes in the
central core and T tubule.

There is an association between thyroid dysfunc-
tion and lymphoma treatment, which usually occurs
after blanket radiotherapy. Chemotherapy seems
to reduce the incidence of hypothyroidism in patients
acted with radiotherapy, because of its immuno-
pressor effect. Radiotherapy and chemotherapy asso-
ciated seems to elevate the incidence of thyroid no-
dules. Probably radiotherapy is associated to hypo-
thyroidism because it compromises thyroid tissue,
leading to cellular destruction, and consequently a
reduction of thyroid follicles, leading to releasing of auto
antibodies against thyroid cells. In the present case,
as the patient was treated only with chemotherapy,
there was not a relation between the lymphoma treat-
ment and the thyroid dysfunction, being a fortuitous association with autoimmune thyroiditis.

The treatment consists on given synthetic thyroid hormone, in the form of thyroxin, and the dosage varies between 100 to 200µg/day. Patients should be evaluated for cardiovascular risks previously to treatment because the risk of acute coronary insufficiency, especially in elderly. Some patients with severe myopathic manifestations may present a worsening in the beginning of the treatment, probably caused by the raise of metabolic demand induced by thyroxin. In these cases, it is recommended the concomitant use of corticotherapy during some time of the treatment, as membrane-stabilizing effect.

In conclusion, the etiology of myopathy in the related case was associated with autoimmune thyroiditis in a patient with previous history of non-Hodgkin lymphoma. There was resolution of the symptoms with three months of treatment in use of thyroxin (150 µg /day). It is an infrequent cause of myopathy, with good prognosis.

REFERENCES