Unusual association of diseases/symptoms

Painful hypoadrenalism

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Correspondence to Dr Chisho Hoshino, girm-hoshino@ohta-hp.or.jp**Summary**

A 61-year-old man presented with diffuse myalgia and arthralgia. The physical examination showed diffuse musculoskeletal tenderness and joint stiffness without the presence of synovitis or arthritis. Nerve conduction study showed combined mild axonal degenerative and demyelinating change. Muscle biopsy analysis showed unspecific mild muscle atrophy with myopathic changes found on electromyography. A diagnosis of isolated adrenocorticotrophic hormone deficiency was made on the basis of endocrinological evaluation. The widespread musculoskeletal pain resolved as a result of administration of physiological dose of hydrocortisone replacement. In a patient with unexplained rheumatic symptoms, adrenocortical insufficiency should be considered in the possible aetiology.

BACKGROUND

Musculoskeletal symptoms associated with endocrine diseases such as myxedema, hyperthyroidism, acromegaly and hyperparathyroidism are known as 'endocrine myopathies'.¹ Muscle weakness and fatigue sometimes associated with myalgia are also common in an excess of exogenous or endogenous corticosteroids.¹ In contrast, clinical manifestations in patients with primary or secondary hypoadrenalism are predominantly fatigue, weakness, gastrointestinal complaints and weight loss. However, although not fully recognised, musculoskeletal symptoms occur in 6–13% of patients with adrenocortical insufficiency,^{2,3} and a variety of rheumatic symptoms such as myalgia, arthralgia, joint stiffness, muscle cramps, low back pain and flexion contracture have been described in the literature to date.^{4–6}

We report a 61-year-old man presenting with musculoskeletal symptoms secondary to isolated adrenocorticotrophic hormone (ACTH) deficiency.

CASE PRESENTATION

A 61-year-old man visited his primary care physician complaining of 8-week history of diffuse myalgia and arthralgia, together with 6-week history of general malaise, anorexia and losing 10 kg in body weight. Despite the patient, suspected of having a progressive rheumatic disease, was advised to immediately undergo an inpatient medical evaluation, he had refused the doctor's instruction. But due to worsening symptoms, he eventually accepted admission to our hospital 3 months after the onset. He had no medical history of musculoskeletal, autoimmune and endocrine diseases. On admission, the blood pressure was 98/70 mm Hg, the heart rate was 60 beats per minute and the body temperature was 36.8°C. Physical examination revealed arthralgia of the wrists and fingers bilaterally without the presence of synovitis or arthritis, diffuse musculoskeletal tenderness and stiffness in the shoulders, elbows, wrists, hips and knees bilaterally, resulting in a gait difficulty. The remainder of physical or neurological findings was uneventful.

INVESTIGATIONS

Laboratory examination showed a white blood cell count of 5400/μl with 4.4% eosinophils (reference range 1–3%), and a haemoglobin of 11.2 g/dl with mean corpuscular volume of 86.8 fl (reference range 83–105 fl). The serum sodium was 134 mEq/l (reference range 135–147 mEq/l) with no other electrolyte abnormalities, fasting glucose 65 mg/dl (reference range 70–109 mg/dl) and creatine kinase 105 IU/l (reference range 50–195 IU/l). Rheumatoid factor, anti-nuclear antibody and anti-Jo-1 antibody were negative. As the low blood pressure, low-grade eosinophilia, normochromic normocytic anaemia, hyponatremia and hypoglycemia raised a suspicion of hypoadrenalism, pituitary-adrenal functions were examined, showing low-normal serum ACTH of 9.4 pg/ml (reference range 9.0–52.0 pg/ml) despite low serum cortisol of 0.4 μg/dl (reference range 4.0–19.2 μg/dl) in basal. Combination stimulation test with corticotrophin-releasing hormone, growth hormone-releasing hormone, thyrotropin-releasing hormone and luteinising hormone-releasing hormone showed blunted response in ACTH, cortisol and thyroid stimulating hormone (TSH) with depressed values, while prolactin, luteinising hormone, follicle stimulating hormone and growth hormone were normal response. Basal serum free triiodothyronine (FT3) and free thyroxine (FT4) were elevated of 7.96 pg/ml (reference range 1.45–3.48 pg/ml) and 3.83 ng/dl (reference range: 0.71–1.85 ng/dl), respectively, with the presence of anti-thyroid peroxidase antibody of 24.5 IU/ml (reference range: <16.0 IU/ml) and anti-thyroglobulin antibody of 124.3 IU/ml (reference range: <28.0 IU/ml). Both TSH receptor antibody and TSH receptor stimulating antibody were negative.

MRI of the pituitary-hypothalamic region showed no abnormalities. As a result of these investigations, the patient was diagnosed as having isolated ACTH deficiency of unknown aetiology. Coexisting thyrotoxicosis was considered to result from an autoimmune thyroiditis (Hashimoto's thyroiditis) accompanied by hypoadrenalism.

Nerve conduction study (NCS) showed combined mild axonal degenerative and demyelinating changes in the

median and tibial nerve with slightly decreased compound muscle action potential, low amplitude and slow nerve conduction. Electromyography (EMG) showed myopathic changes in the biceps and quadriceps with spontaneous fibrillation and positive sharp potential, together with shortened duration and decreased amplitude of polyphasic motor unit potential during voluntary contraction. Muscle biopsy analysis in the quadriceps showed mild atrophy of type 2 fibre without the presence of inflammatory infiltrate, vasculitis, granulomatous lesion and ragged red fibre.

DIFFERENTIAL DIAGNOSIS

- ▶ Endocrine myopathy associated with thyrotoxicosis
- ▶ Amyotrophic lateral sclerosis
- ▶ Inflammatory demyelinating polyradiculoneuropathy
- ▶ Muscular dystrophy
- ▶ Myasthenia gravis
- ▶ Dermatomyositis/polymyositis
- ▶ Sarcoid myopathy
- ▶ Polymyalgia rheumatica
- ▶ Temporal arteritis
- ▶ Fibromyalgia
- ▶ Osteomalacia.

TREATMENT

Oral prednisolone 10 mg once a day was administered for 7 days and then switched to a twice daily regimen of hydrocortisone 15 mg/day.

OUTCOME AND FOLLOW-UP

Nausea and anorexia resolved 7 days after initiation of steroid therapy. Subsequently, diffuse myalgia and arthralgia gradually improved without any analgesics or muscle relaxants, resulting in being fully ambulatory within 30 days. Serum thyroid function including TSH, FT3 and FT4 normalised without further treatment. The patient has been followed up for over 18 months with good clinical course.

DISCUSSION

The clinical features of isolated ACTH deficiency

Isolated ACTH deficiency can be due to an autoimmune, congenital, vascular or anatomical abnormality or damage in the pituitary-hypothalamic region.⁷ However, in the present case, no apparent cause was identified as evidenced by the MRI that showed no possible abnormality such as empty sella, partial infarction, granulomatous lesion, neoplasm or lymphocytic hypophysitis in this region. Isolated ACTH deficiency has been associated with various autoimmune disorders including Graves' disease, Hashimoto's thyroiditis, myasthenia gravis, type 1 diabetes mellitus and autoimmune adrenalitis.⁷ In the present case, an increasing autoimmune activity due to hypoadrenalism possibly induced thyrotoxicosis, resulting in further exacerbation of adrenocortical insufficiency.⁸ However, his symptoms were less likely to be a direct result of the thyrotoxicosis given that thyroid function was normal when he first visited his primary care physician complaining of persistent myalgia and arthritis.

The clinical features of hypoadrenalism induced musculoskeletal symptoms

The underlying aetiology of musculoskeletal symptoms associated with adrenocortical insufficiency includes isolated ACTH deficiency, hypopituitarism and Addison's disease.^{4,5} According to previous reports, its features are as follows: the results of neuromuscular investigations including NCS, EMG or muscle biopsy analysis are inconsistent and unspecific⁴; however, the longer the musculoskeletal symptoms persist, the more likely these neuromuscular investigations show abnormal results⁴; corticosteroid administration can provide complete or partial symptomatic relief with an improvement in the neuromuscular investigations^{4,5}; the longer the treatment is delayed, the longer it may take before the symptomatic resolution, especially in cases with flexion contracture.⁶

The pathogenesis of hypoadrenalism induced musculoskeletal symptoms

A true cause-and-effect relationship between adrenocortical insufficiency and musculoskeletal symptoms remains to be elucidated. However, the association between corticosteroid and neuromuscular system has been described in the literatures.

Corticosteroid and skeletal muscle wasting

Wada *et al*⁹ reported that in an isolated ACTH deficiency patient after corticosteroid treatment, increased muscle volume calculated by the total cross-sectional muscle area of CT was noted with both increased proportion and mean diameter of muscle fibre in type 1 and type 2A, suggesting that skeletal muscle wasting due to corticosteroid deficiency may induce the limitation of joint range of motion. Thus, physiologic dose corticosteroid, defined as endogenous cortisol production rates of 5–10 mg/m²/day (equivalent to the oral administration of 15–25 mg hydrocortisone or cortisol),¹⁰ may have an anabolic effect on the skeletal muscle to maintain metabolic functions or an activating effect on the motor neurons innervating specific muscle fibre,⁹ whereas supra-physiologic dose of corticosteroid is generally known to have a catabolic effect on skeletal muscle. However, musculoskeletal widespread tenderness or arthralgia of the present case is not completely explained by the skeletal muscle wasting alone. We therefore review studies on the association between corticosteroid and pain condition in terms of the hypothalamic-pituitary-adrenal (HPA) axis or the nervous network.

Hypothalamic-pituitary-adrenal (HPA) axis and chronic pain

Chronic fatigue syndrome (CFS) is a condition with the presence of prolonged fatigue, depressed mood and marked disability, together with several somatic symptoms such as myalgia and arthralgia,¹¹ which are markedly similar to those found in adrenocortical insufficiency. Furthermore, these symptoms can be induced by withdrawal from a condition with excess of endogenous cortisol.¹² Interestingly, in CFS, dysfunction of the HPA axis has been described with the effects of low-dose hydrocortisone therapy.¹³ In such cases, impaired HPA axis might result in a failure to adequately mount a stress response, which predisposed to high pain sensitivity.^{14–16}

Corticosteroid and the nervous network

The pain sensation is the result of a complex nervous network from the sensory input via the spinal cord to central nervous system (CNS). Cortisol may influence symptoms through CNS neurotransmitters including serotonin¹⁷ and norepinephrine (NE).¹⁸ The NE coeruleospinal system appears to play a significant role in spinal nociceptive processing.¹⁹ In addition, cortisol may also influence pain processing through corticosteroid receptors in the spinal cord dorsal horn, which play a crucial role in the mediation of nociceptive pain transmission.²⁰

Polymorphisms and individual variation

The degree to which hypoadrenalism influences neuromuscular system varies among individuals given that musculoskeletal symptoms due to adrenocortical insufficiency are less common. The polymorphisms of the corticosteroid receptor gene may be associated with the variability in corticosteroid sensitivity and may affect the body composition, muscle mass and muscle strength,²¹ which could explain the clinical individual variation.

CONCLUSION

In cases with musculoskeletal symptoms, the possibility of an endocrine aetiology should be considered. Especially, in hypoadrenalism, musculoskeletal abnormalities can be antecedent or predominant signs, although its true pathogenesis remains to be elucidated. Thus, adrenocortical insufficiency including isolated ACTH deficiency, hypopituitarism, and Addison's disease should be in the differential diagnosis for unexplained musculoskeletal symptoms because delayed diagnosis can be fatal. Adrenocortical insufficiency can be complicated by a variety of autoimmune disorders including Hashimoto's thyroiditis, but corticosteroid replacement therapy should be the first priority.

Learning points

- ▶ Physician must be alert to the possibility of an endocrine aetiology in cases with musculoskeletal symptoms.
- ▶ Musculoskeletal abnormalities can be antecedent or predominant signs in adrenocortical insufficiency.
- ▶ In isolated ACTH deficiency, autoimmune thyroiditis can be complicated and may result in further exacerbation of adrenocortical insufficiency, especially if presenting as thyrotoxicosis.
- ▶ Administration of corticosteroid replacement therapy should be the first priority and can resolve musculoskeletal symptoms associated with hypoadrenalism without any analgesics or muscle relaxants.

Acknowledgements The authors thank Dr Kiyomi Yamane and Dr Akeshi Morimatsu, Department of Neurology, Ohta-Atami Hospital, for their help with neuromuscular investigations.

Competing interests None.

Patient consent Obtained.

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Hoshino C, Satoh N, Narita M, Kikuchi A, Inoue M. Painful hypoadrenalism. *BMJ Case Reports* 2011;10.1136/bcr.01.2011.3735, date of publication

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