

Case Report Article

Musculoskeletal symptoms and neurological investigations in adrenocortical insufficiency: A case report and literature review

H. Kinoshita¹, S. Mizutani^{1,2}, K. Sei¹, M. Shimizu¹, M. Yasuda¹, T. Ohkubo^{1,2}, H. Tomimitsu², T. Kamata^{1,2}, F. Yakushiji¹

¹Department of Internal Medicine, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan;

²Department of Neurology and Neurological Science, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

Abstract

Objectives: Various forms of adrenocortical insufficiency can cause musculoskeletal symptoms such as muscle pain, tautness of the limbs, arthralgia, and flexion contractures. However, the findings of neurological investigations are inconclusive and have not been well summarized. **Methods:** We report the case of a 61-year-old man with isolated adrenocorticotrophic hormone deficiency who presented with musculoskeletal symptoms, including flexion contractures. We performed three neurological investigations: nerve conduction studies, electromyography, and muscle biopsy analysis. Further, we reviewed reports of 16 patients with various forms of adrenocortical insufficiency and musculoskeletal symptoms by considering the findings of these three investigations. **Results:** From the literature review, we found that (a) analysis of muscle biopsy is the most sensitive technique, followed by electromyography and then nerve conduction studies; and (b) the longer the duration of the musculoskeletal symptoms, the greater the incidence of abnormal findings with all three techniques. **Conclusions:** Physicians may prioritize neurological investigations, depending on these findings.

Keywords: Musculoskeletal Symptoms, Flexion Contractures, Neurological Investigations, Adrenocortical Insufficiency, Isolated Adrenocorticotrophic Hormone Deficiency

Introduction

Various forms of adrenocortical insufficiency can cause musculoskeletal symptoms¹. Anderson and Lyall reported the case of a patient with Addison's disease who presented with stiffness and subsequent pain in the knees. Thereafter, both knees were in semiflexion, and movements were slow because of spasms in the quadriceps and hamstring muscles². Gallavan and Steegman described the cases of 2 patients with hypopituitarism who were unable to straighten their knees³. Steinberg et al. reported the case of a patient with isolated adrenocorticotrophic hormone (ACTH)

deficiency with muscle pain and arthralgia⁴. When adrenocortical insufficiency is not appropriately treated, the musculoskeletal symptoms may spontaneously progress to flexion contractures⁵. However, the symptoms can be reversed by replacement therapy with glucocorticoids but not mineralocorticoids⁶.

Nonetheless, because the symptoms of adrenocortical insufficiency were not adequately documented, an article entitled "Flexion contractures: A forgotten symptom in Addison's disease and hypopituitarism" was published in 1986⁷. Thereafter, in a standard textbook of endocrinology, the frequency of musculoskeletal symptoms such as muscle pain or arthralgia in patients with adrenocortical insufficiency was recorded at 6-13%¹.

Although patients with adrenocortical insufficiency develop symptoms of joint disease, there is no clinical, laboratory, or radiographic evidence of joint disease; further, neurological signs are also absent⁸. Many reports have described the results of neurological investigations such as nerve conduction studies (NCSs), electromyography (EMG), or muscle biopsy analysis^{7,9-22}; however, these results are inconclusive⁸ and have not been well summarized.

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Corresponding author: Hiroyuki Kinoshita, M.D., Ph.D., 4-23-15 Koutoh-bashi, Sumida-ku, Tokyo 130-8575, Japan
E-mail: hkinoshita-ky@umin.ac.jp

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In the present study, we performed NCSs, EMG, and muscle biopsy analysis for a patient with isolated ACTH deficiency who presented with musculoskeletal symptoms. In addition, we reviewed previous articles to examine the association between the findings of neurological investigations and musculoskeletal symptoms in patients with adrenocortical insufficiency.

Patients and methods

a. Case Report

A 61-year-old man was brought to the emergency department of our hospital in August 2008. He presented with general fatigue, appetite loss, and body weight loss that had persisted since April 2008. In addition, he reported that he had been experiencing tautness of the lower limbs with increasing severity since July 2008. In August 2008, he developed muscle pain and arthralgia in the lower limbs as well as flexion contractures of the knees and hips, and could not stand without assistance.

On physical examination, the findings of a manual muscle test and the deep tendon reflexes were normal. Muscle contractures of the hips and knees were evident. The patient experienced spontaneous and grasp pain in both femurs on attempting to straighten his lower limbs. A routine laboratory examination revealed several abnormalities, including eosinophilia (a white blood cell count of 12.9×10^9 cells/L with a differential count of 43.8% neutrophils, 10.8% lymphocytes, and 38.0% eosinophils), hyponatremia (Na concentration, 129 mEq/L), and hypoglycemia (glucose concentration, 66 mg/dL). The creatine kinase (CK) concentration was normal (70 U/L).

On the basis of these results, we considered adrenocortical insufficiency, eosinophilia-myalgia syndrome, and stiff-man syndrome in the differential diagnosis. The results of NCSs and EMG were normal. Analysis of a muscle biopsy specimen obtained from the quadriceps femoris revealed no eosinophil infiltration but a slight decrease in the number of type 1 fibers. Endocrine analysis revealed the following levels: ACTH, 7.0 pg/ml (reference range, 9.0-52.0 pg/mL); cortisol, 0.5 μ g/dL (reference range, 4.5-21.1 μ g/dL); urinary cortisol, 12.0 μ g/day (reference range, 26.0-187.0 μ g/day); urinary 17-hydroxycorticosteroid (17-OHCS), <3.4 mg/day (reference range, 3.4-12.0 mg/day); and urinary 17-ketosteroid (17-KS), 3.7 mg/day (reference range, 4.6-18.0 mg/day). No response was detected in the corticotrophin-releasing hormone (CRH) test, and the following hormone levels were recorded: ACTH (pg/ml), 8.1 (pre), 8.6 (30 min), 9.2 (60 min), 8.1 (90 min), and 8.4 (120 min); and cortisol (μ g/dL), 0.6 (pre), 0.7 (30 min), 0.6 (60 min), 0.6 (90 min), and 0.5 (120 min). A low response was detected in the rapid ACTH test, with the following hormone levels: cortisol (μ g/dL), 0.5 (pre), 3.4 (30 min), and 5.0 (60 min). A normal response was detected in the continuous ACTH test, with the urinary cortisol levels (μ g/day) at 12.0 (pre), 182.7 (1 day), 305.0 (2 days), and 342.9 (3 days). The other hormones were detected at almost normal levels: plasma renin activity, 1.6 ng/mL/hr (reference range, 1.0-2.0 ng/mL/hr); aldosterone, 4.8 ng/dL (reference range, 3.6-24.0 ng/dL); thyroid stimulating hormone, 1.88

μ U/mL (reference range, 0.35-4.94 μ U/mL); free triiodothyronine, 2.20 pg/mL (reference range, 1.71-3.71 pg/mL); free tetraiodothyronine, 0.72 ng/dL (reference range, 0.70-1.48 ng/dL); growth hormone, 3.5 ng/mL (reference range, <0.17 ng/mL); insulin-like growth factor I, 28.8 ng/mL (reference range, 106-398 ng/mL); prolactin, 24.3 ng/mL (reference range, 3.6-12.8 ng/mL); luteinizing hormone, 20.0 mIU/mL (reference range, 1.2-7.1 mIU/mL), and follicle stimulating hormone, 16.0 mIU/mL (reference range, 2.0-8.3 mIU/mL). Computed tomography of the pituitary gland revealed an empty sella. No antipituitary antibodies were detected. After further examination, we established a diagnosis of isolated ACTH deficiency.

We initiated treatment with hydrocortisone at a dose of 30 mg/day (20 mg in the morning and 10 mg in the evening). Within a day of this therapy, the patient's musculoskeletal symptoms dramatically improved. After 3 days of the treatment, he was able to stand and walk without assistance, despite some remnant tautness in the lower limbs. The patient's eosinophilia, hyponatremia, hypoglycemia, general fatigue, and appetite loss were also ameliorated. The hydrocortisone dose was then gradually reduced to 15 mg/day (10 mg in the morning and 5 mg in the evening), and this dose did not aggravate his general condition and musculoskeletal symptoms.

b. Literature Review

We reviewed previous articles on neurological investigations such as NCSs, EMG, and muscle biopsy analysis for musculoskeletal symptoms associated with adrenocortical insufficiency^{7,9-22}. Thus far, there have been 16 reports on 16 patients in this regard, including our present report. Apart from the present report, the literature retrieved consisted of 15 full-length articles^{7,9-22}. In the literature review, we focused on (a) preferred neurological investigations for patients with adrenocortical insufficiency, and (b) the association between the duration of musculoskeletal symptoms and abnormal findings in neurological investigations.

Results

The results of our literature review are shown in Table 1.

a. Characteristics of Patients

The mean (standard deviation [SD]) age of the patients was 52.3 (11.0) years (range, 26-66 years). Of the 16 patients, 12 (75.0%) were men and 4 (25.0%) were women. The underlying etiology was isolated ACTH deficiency in 6 (37.5%) patients, hypopituitarism in 7 (43.8%), and Addison's disease in 3 (18.8%). These findings reinforced the observation that various forms of adrenocortical insufficiency can cause musculoskeletal symptoms¹.

b. Neurological investigations

NCSs, EMG, and muscle biopsy analysis were performed in 10, 14, and 8 patients, respectively, and revealed abnormal findings in 4 (40.0%), 6 (42.9%), and 5 (62.5%) patients, respectively. Thus, muscle biopsy analysis was the most sensi-

| Age/Sex | Etiology | Duration | NCS | EMG | Muscle Biopsy | Reference |
|---------|-----------------|-----------|--------------------------------|------------------------|--|-----------|
| 44/F | Addison | 2 weeks | normal | myogenic | - | 9 |
| 56/M | IAD | 1 month | - | normal | normal | 10 |
| 61/M | IAD | 1 month | normal | normal | number of type1 fiber ↓ | our case |
| 66/M | hypopituitarism | 2 months | abnormal | denervation potential | - | 11 |
| 60/M | IAD | 3 months | normal | normal | atrophy of type2B fiber number of type1, 2A fiber ↓ | 12 |
| 26/M | Addison | 3 months | - | normal | - | 13 |
| 57/M | hypopituitarism | 3 months | normal | normal | atrophy of: type2 fiber | 14 |
| 37/M | hypopituitarism | 6 months | - | myogenic | normal | 15 |
| 45/M | Addison | 6 months | - | - | normal | 16 |
| 64/M | hypopituitarism | 8 months | - | normal | fiber size variation | 17 |
| 55/M | IAD | 9 months | CMAP, SNAP amp ↓ MCV, SCV ↓ | normal | atrophy of type1 fiber number of type2 fiber ↓ | 18 |
| 51/F | hypopituitarism | 16 months | normal | continuous firing | - | 19 |
| 64/M | hypopituitarism | 2 years | normal | normal | - | 7 |
| 57/M | IAD | 2 years | CMAP, SNAP amp ↓ MCV, SCV ↓ | - | - | 20 |
| 51/F | IAD | 3 years | - | neurogenic myogenic | - | 21 |
| 42/F | hypopituitarism | 4years | CMAP amp ↓ | continuous firing | - | 22 |

Abbreviations: IAD; isolated adrenocorticotrophic hormone deficiency; NCS; nerve conduction study; CMAP; compound muscle action potential; SNAP; sensory nerve action potential; amp; amplitude; MCV; motor nerve conduction velocity; SCV; sensory nerve conduction velocity; EMG; electromyography.

Table 1. Duration with musculoskeletal symptoms such as muscle pain, tautness of limbs, arthralgia, or flexion contracture in adrenocortical insufficiency and neurological investigations.

tive technique, followed by EMG and then NCSs.

The detailed results of the three neurological investigations were as follows. NCSs yielded normal findings^{7,9,12,14,19}; abnormalities in the compound muscle action potential or motor nerve conduction velocity^{18,20,22}; or abnormalities in the sensory nerve action potential or sensory nerve conduction velocity^{18,20}. EMG revealed normal findings^{7,10,12-14,17,18}, neurogenic changes²¹, or myogenic changes^{9,15,21}. Muscle biopsy analysis yielded normal findings^{10,15,16} or various forms of muscle fiber abnormalities^{12,14,17,18}. These results reinforced the previous findings that neurological investigations are inconclusive in cases of adrenocortical insufficiency with musculoskeletal symptoms⁸.

c. Duration of musculoskeletal symptoms and abnormal findings in neurological investigations

The association between the duration of musculoskeletal symptoms and abnormal findings in all three techniques was as follows. When NCSs, EMG, and muscle biopsy analysis were performed within six months from the onset of musculoskeletal symptoms, abnormal results were obtained in 1 of 5 (20.0%), 3 of 8 (37.5%), and 3 of 6 (50.0%) patients, respectively. When these neurological investigations were performed 8 months after the onset of musculoskeletal symptoms, abnormal results were

obtained in 3 of 5 (60.0%), 3 of 6 (50.0%), and 2 of 2 (100%) patients, respectively. The results revealed that the longer the duration of musculoskeletal symptoms, the greater the incidence of abnormal findings with all three techniques.

Discussion

We report the case of a patient with isolated ACTH deficiency who presented with musculoskeletal symptoms. We performed three neurological investigations to assess the condition. The results of NCSs and EMG were normal. Muscle biopsy analysis revealed a slight decrease in the number of type 1 fibers. The musculoskeletal symptoms dramatically improved with hydrocortisone treatment. From the literature review, we found that (a) muscle biopsy analysis is the most sensitive technique, followed by EMG and then NCSs; and (b) the longer the duration of musculoskeletal symptoms, the greater the incidence of abnormal findings with all three techniques.

a. Clinical applications of the three techniques for musculoskeletal symptoms in adrenocortical insufficiency

In clinical practice, adrenocortical insufficiency may or may not be considered in the differential diagnosis. In cases where

(i) adrenocortical insufficiency is not considered, the neurological investigation technique adopted would depend on the patient's neurological symptoms. In general, a noninvasive technique is preferred; therefore, NCSs would be selected over EMG, and EMG over muscle biopsy. These neurological investigations may provide insights into the pathogenesis of musculoskeletal symptoms in cases of adrenocortical insufficiency.

In cases where (ii) adrenocortical insufficiency is considered, the first step would be to evaluate the ACTH-adrenal axis. On the other hand, improvements in the findings of NCSs^{18,20} and EMG^{11,15,19,22} have been reported after glucocorticoid administration in patients with adrenocortical insufficiency. Therefore, clinical practitioners may perform neurological investigations to verify the effectiveness of the treatment. According to our findings, muscle biopsy analysis is the most sensitive technique for detecting abnormalities, followed by EMG and then NCSs. However, the order of these techniques is reversed in terms of invasiveness.

On the basis of these results, we recommend that NCSs may be considered as the first option. If NCSs reveal abnormal findings, no further neurological investigations may be required, because improvements in NCSs would indicate the effectiveness of the treatment. EMG may be the second option because it is more sensitive than NCSs. If EMG shows abnormal findings, no further investigations may be required. Finally, muscle biopsy analysis – the most sensitive technique – may be adopted. When the musculoskeletal symptoms have persisted for a prolonged duration before diagnosis of adrenocortical insufficiency, even NCSs may reveal may reveal abnormal findings because the longer the duration of musculoskeletal symptoms, the greater the incidence of abnormal findings with all 3 techniques. However, early diagnosis of adrenocortical insufficiency is essential because the longer the delay in diagnosis, the longer the time required for the resolution of musculoskeletal symptoms⁸. Physicians treating patients with musculoskeletal symptoms should be aware of the relationship between these symptoms and adrenocortical insufficiency.

b. Remnant and new musculoskeletal symptoms after glucocorticoid administration

To the best of our knowledge, the musculoskeletal symptoms improved in all patients with adrenocortical insufficiency who were administered glucocorticoids. However, as in the present case, some degree of muscular tautness often persists^{17,18,22}. Wada studied the improvements in the muscle condition after glucocorticoid administration in a patient with isolated ACTH deficiency, and speculated that the improvement in the thickness of the muscle fiber is the former and that in the length of the muscle fiber is the latter¹². This may explain the remnant tautness experienced by some patients. It was reported that 3% patients with adrenocortical insufficiency who have been treated with glucocorticoids present with musculoskeletal symptoms such as painful and debilitating contractures of the thigh muscles and tendons⁶. In short, both adrenocortical insufficiency and glucocorticoid administration can cause similar musculoskeletal symptoms. Physicians should consider these contradictory phenomena.

c. Mechanisms of musculoskeletal symptom development in adrenocortical insufficiency

Various mechanisms have been proposed to explain the development of musculoskeletal symptoms. Wisenbaugh and Heller implicated electrolyte abnormalities in this process¹⁶. However, Slater performed electrolyte composition examinations and found that the sodium and potassium content of both the affected and unaffected muscles was normal¹⁷. Gruener and Stern studied the effects of corticosteroids on muscle-membrane excitability in order to identify the cause of these symptoms²³. Nevertheless, the underlying mechanism has not been conclusively identified thus far.

d. Differences in the association between glucocorticoids and the neuromuscular system among individuals

Not all patients with adrenocortical insufficiency exhibit musculoskeletal symptoms. Further, various symptoms and abnormalities may be identified during neurological investigations. Thus, the association between glucocorticoids and the neuromuscular system may vary among individuals.

In the dbSNP database, approximately 800 single nucleotide polymorphisms for the glucocorticoid receptor gene have been recorded. On combining with glucocorticoids, the glucocorticoid receptor functions as a transcription factor to regulate the transcription of many genes. Further, genes regulated by the glucocorticoid-glucocorticoid receptor complex exhibit many polymorphisms. The whole-genome expression profiles of glucocorticoid receptor-null mice and wild-type mice have been analyzed by microarray analysis: the results revealed that genes involved in cell proliferation and cell division were significantly downregulated, whereas those involved in carbohydrate metabolism and kinase activity were significantly upregulated²⁴. We infer that the polymorphisms of the glucocorticoid receptor gene and the relevant affected pathways determine the difference among individuals with regard to the relationship between glucocorticoids and the neuromuscular system. These may explain why individuals show variations in the neurological symptoms, symptom frequency, and abnormalities detected in neurological investigations. Further research on this topic should be conducted from the viewpoint of pharmacogenetics.

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