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CASE REPORT

Rapid conversion of autoimmune hypophysitis to an empty sella with immediate lowering of the serum IgG4 level

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Abstract

An 87-year-old man was admitted with fatigue, anorexia, vomiting, urinary incontinence, and a depressive state. His consciousness was evaluated as a 13 on the Glasgow Coma Scale (E4V3M6), and he had a body temperature of 36.4°C, a blood pressure of 91/60 mmHg, and a heart rate of 88 beats/min. General laboratory data were unremarkable except for a mildly elevated serum creatinine level. The plasma levels of growth hormone, luteinizing hormone, and follicle stimulating hormone were depressed. On the other hand, the prolactin level was elevated, and the corticotropin, cortisol, and thyrotropin levels were within the reference ranges. Cranial magnetic resonance imaging (MRI) revealed the marked swelling of the pituitary gland and the infundibular stalk, and the serum immunoglobulin G4 (IgG4) level was elevated (2.85 g/L; reference range, 0.048–1.05 g/L). Accordingly, a diagnosis of IgG4-related autoimmune hypophysitis (AH) was made. The patient responded well to glucocorticoid therapy, but the presence of diabetes insipidus was revealed and was subsequently controlled using desamino-D-arginine vasopressin (DDAVP). To our surprise, an empty sella was apparent on an MRI examination performed on Day 12. The patient's serum IgG4 level had decreased in a log-linear manner with a half-life of 30 days, which was comparable to the half-life of IgG4 in control subjects (21 days). At a 16-month follow-up examination, no substantial changes in the morphology or function of the pituitary gland were noted. In conclusion, an empty sella developed within 12 days after the clinical onset of AH in the present case, suggesting that an empty sella may be the direct outcome of AH. The conversion of AH to an empty sella was associated with an immediate shutdown of IgG4 overproduction.

Abbreviations:

AH	- autoimmune hypophysitis
DDAVP	- desamino-D-arginine vasopressin
DI	- diabetes insipidus
IgG4	- immunoglobulin G4
MRI	- magnetic resonance imaging

INTRODUCTION

Empty sella syndrome (ESS) and autoimmune hypophysitis (AH) have been considered closely related entities on the basis of the high prevalence of positive pituitary antibodies in patients with ESS (Komatsu *et al.* 1988; Lupi *et al.* 2011). Recently, it has been argued that ESS may be the final outcome of AH (Klein & Fehm, 2005; Karaca *et al.* 2009; Gao *et al.* 2013). However, this hypothesis remains to be proven, since it was based on the observation that patients incidentally diagnosed as having ESS had a remote history of AH (Klein & Fehm, 2005; Karaca *et al.* 2009; Gao *et al.* 2013).

MATERIALS AND METHODS

An 87-year-old man was admitted with fatigue, anorexia, vomiting, urinary incontinence and a depressive state. He was conscious (Glasgow Coma Scale, 13 [E4V3M6]), and he had a body temperature of 36.4 °C, a blood pressure of 91/60 mmHg, and a regular heart rate of 88 beats/min.

General laboratory data were unremarkable except for a mildly elevated serum creatinine level (172 μmol/L). Upon admission, cranial magnetic resonance imaging (MRI) revealed the diffuse swelling of the pituitary gland and the infundibular stalk (Figure 1A), suggesting the presence of hypophysitis. On Day 3, the patient's hypotension and vomiting persisted, and he developed aspiration pneumonia; consequently, 100 mg/day of hydrocortisone was administered, together with an antibiotic and fluids. This treatment was initiated prior to receiving a report on the patient's endocrine data, so the diagnosis of hypopituitarism was a presumptive one at this stage.

Endocrine data based on a blood sample obtained upon admission (before the administration of hydrocortisone) revealed a reduction in growth hormone (0.05 ng/mL; reference range, lower than 2.47 ng/mL), luteinizing hormone (<0.1 mIU/mL; reference range, 0.79–5.72 mIU/mL), and follicle stimulating hormone (1.28 mIU/mL; reference range, 2.0–8.3 mIU/mL) and an elevation of prolactin (44.3 ng/mL; reference range, 4.3–13.7 ng/mL). The levels of thyrotropin and free triiodothyronine were within the reference ranges, but that of free thyroxine was slightly suppressed at 0.76 ng/dL (reference range, 0.9–1.7 ng/dL). The plasma corticotropin level (56.3 pg/mL; reference range, 7.2–63.3 pg/mL) and the cortisol level (9.0 μg/dL; reference range, 6.2–19.4 μg/dL) were not depressed. The serum immunoglobulin G4 (IgG4) level was elevated (285 mg/dL; reference range, 4.8–105 mg/dL). Together, a diagnosis of IgG4-related AH with hypopituitarism (Leporati *et al.* 2011; Caturegli *et al.* 2005) was made. The patient's symptoms and pneumonia began to subside on Day 5, but diabetes insipidus (DI) became clinically overt and was controlled by the administration of desamino-D-arginine vasopressin (DDAVP). The administration of hydrocortisone (100 mg/day, intravenously) was continued until Day 11, at which time the treatment was switched to 10 mg of prednisolone administered orally for 8 days. The glucocorticoid dosage was further tapered thereafter, with a final oral dosage of 5 mg of hydrocortisone. At a 16-month follow-up examination,

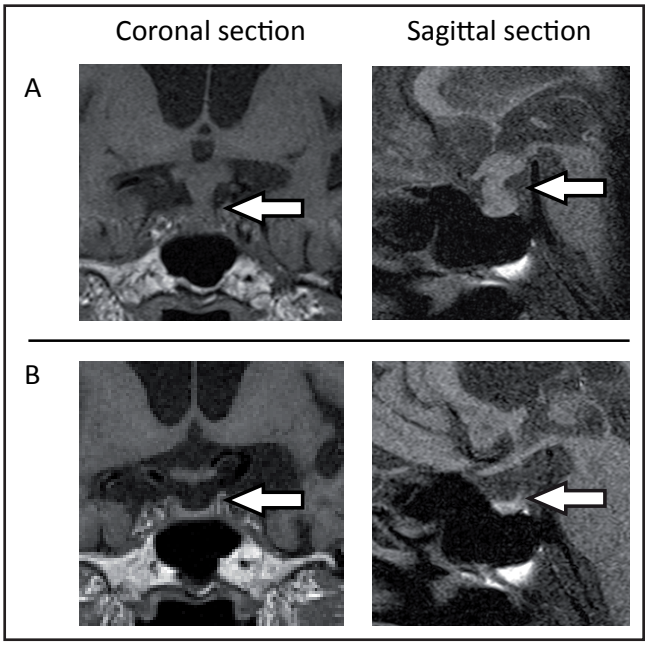

Fig. 1. Cranial MRI (Non-enhanced T1-weighted image). A) Day 0; B) Day 12. The left panels are coronal sections and the right panels are sagittal sections. The arrows indicate the marked swelling of the pituitary gland and the tubeloinfundibular stalk on Day 0 (A) and the empty sella on Day 12 (B). A high intensity of the neurohypophysis was absent throughout.

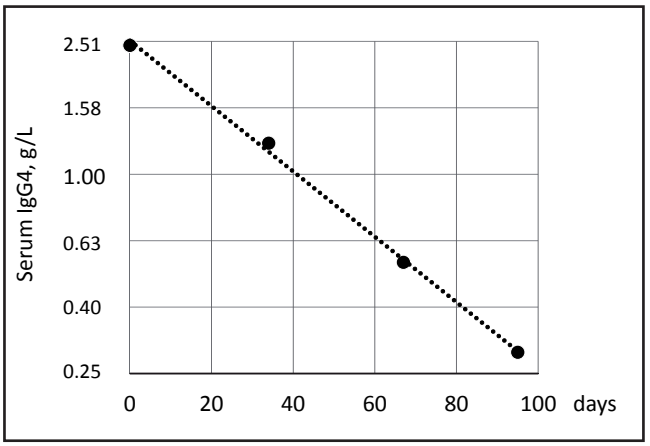

Fig. 2. Temporal profile of the reduction in the serum IgG4 level. The ordinate indicates the serum IgG4 level after the subtraction of 41 mg/dL (0.41 g/L), which is the median value for control Japanese subjects (Hamano *et al.* 2001). The abscissa shows the days from admission. Note that the graph is semilogarithmic. The regression line is $\log_{10}(IgG4) = 2.40 + (-0.01) \cdot day$, R^2=–0.999, p<0.001. The calculated half-life was 30 days.

the endocrine data remained unchanged qualitatively (i.e., partial hypopituitarism with elevated prolactin). The patient remained in good condition while orally receiving 5 mg/day of hydrocortisone and 30 μg/day of DDAVP.

To our surprise, a repeated MRI performed on Day 12 revealed an empty sella (Figure 1B). No substantial change in the morphology of the pituitary gland or the stalk has been observed as of the last follow-up MRI examination, which was performed 14 months after the initial admission. Interestingly, the serum IgG4 concentration decreased in a log-linear manner, with a half-life of 30 days during the initial 95 days (Figure 2). The serum IgG4 level had once again increased to 157 mg/dL at the time of the final follow-up examination (16 months).

DISCUSSION

In this patient with IgG4-related AH (Leporati *et al.* 2011; Caturegli *et al.* 2005), a very rapid conversion of AH to an empty sella within 12 days was confirmed. Other possible causes of acute ESS, such as pituitary apoplexy, were excluded based on the obvious absence of typical clinical signs and symptoms and the MRI findings. Therefore, in this case, AH per se definitively converted to an empty sella. In other words, ESS was the direct outcome of AH. Interestingly, the half-life of the reduction in the serum IgG4 level was 30 days, which was very close to the corresponding value (21 days) in control subjects (Vidarsson *et al.* 2014). This finding strongly suggests that an almost complete shutdown of IgG4 overproduction occurred simultaneously with the conversion of AH to ESS. The administration of glucocorticoid may have caused the amelioration of hypophysitis and promoted the conversion of AH to ESS and the rapid reduction in the IgG4 level.

Although the occurrence of ESS at 45 days after the clinical onset of possible hypophysitis has been reported (Gao *et al.* 2013), evidence of the autoimmune nature of the pituitary lesion was not obtained. In other case reports suggesting that ESS may be the final outcome of AH, the interval between the clinical recognition of hypophysitis and the diagnosis of ESS was 1 year or longer, and it was more than 10 years in some cases (Klein & Fehm, 2005; Karaca *et al.* 2009). Therefore, the causality of AH for ESS was only weakly suggested, if at all. Also, laboratory data indicating the presence of autoimmune abnormalities was lacking in these cases (Klein & Fehm, 2005; Karaca *et al.* 2009), so whether an autoimmune abnormality was involved in the etiology of the pituitary lesion was uncertain. Usually, the diagnosis of mild AH is difficult, and AH may often be unrecognized unless a cranial MRI examination targeting the pituitary gland is performed. The same is true for ESS (De Marinis *et al.* 2005). We believe that the present case supports the hypothesis that AH might be a common cause of ESS.

In summary, ESS developed as soon as 12 days after the clinical onset of AH in an elderly patient. Simultaneously, a rapid reduction in the serum IgG4 level occurred. This observation of the immediate transition from AH to ESS definitively establishes a link between these two conditions, i.e., ESS was undoubtedly the outcome of AH. To elucidate the causal role of AH for ESS in general, a prospective analysis of a large number of patients with AH is warranted.

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