
FUMIO OTSUKA, SATOSHI MIZOBUCHI*, TOSHI OGURA, KENJI SATO*, MASATAKA YOKOYAMA* AND HIROFUMI MAKINO

Abstract. We report the case of a 19-year-old man with pituitary gigantism due to growth hormone-producing pituitary macroadenoma. The patient complained of recurrent headache and excessive growth spurt since age 15. Octreotide administration was initiated following transsphenoidal pituitary adenomectomy. Octreotide injection for 4 years efficaciously reduced the size of remnant adenoma as well as serum growth hormone levels. Notably, octreotide exhibited a potent analgesic effect on his intractable cluster headache that has continued even after reduction of the adenoma volume. The analgesic effect lasted 2 to 6 hours after each injection and no tachyphylaxis to octreotide appeared during 4-year treatment. To characterize the headache and the pain intensity, analgesic drugs including octreotide, lidocaine, morphine and thiopental were tested using a visual analogue scale (VAS) evaluation, with the result that octreotide exhibited a prompt and complete disappearance of the headache. Headache relief was in part reproduced by morphine injection (56% reduction) but not by lidocaine or thiopental. The present case suggests that the intractable headache associated with pituitary gigantism is possibly related to the endogenous opioid system. Thus, the headache control by octreotide is clinically helpful for continuation of the self-injection regimen.

Key words: Headache, Octreotide, Opioid receptor, Pituitary gigantism, Visual analogue scale

THE beneficial effects of octreotide are recognized in acromegaly caused by pituitary adenomas [1]. However, the long-term effect of octreotide has not been well documented in pituitary gigantism because of its extremely rare incidence compared with acromegaly [2]. We here present a therapeutic experience regarding pituitary gigantism, which was treated with octreotide injection for four years after transsphenoidal surgery. In the present report, we specifically evaluated the analgesic effect of octreotide regarding the chronic headache associated with pituitary gigantism.

Case Presentation

A 19-year-old Japanese man who complained of recurrent headache, prolonged growth spurt and increases in foot length and body weight was consulted. His growth velocity had become remarkable since age 15. His height was 164 cm (+1 SD), 178 cm (+2 SD), 186 cm (>+2 SD), 194 cm (>+2 SD) at 13, 15, 16, and 18 years old (relative to the Japanese growth chart), respectively. On admission, he was 208 cm tall, 115.6 kg body weight (body mass index, 27.6 kg/m²) and 33 cm of foot size. Acromegalic features included bulging forehead and jaw, with little enlargement of nose and tongue, although radiological examination disclosed mild acromegalic changes of finger tip and heel pad thickness. Cranial magnetic resonance imaging (MRI) revealed a pituitary tumor partially enhancing by gadolinium, occupying the sellar region with extension to optic chiasm and right cavernous...
Serum growth hormone (GH) and insulin-like growth factor (IGF)-1 levels were markedly elevated (96.5 ng/ml and 1064.7 ng/ml; normal, 0.1–2.9 and 219–509, respectively). GH levels were paradoxically increased (~1.5 fold) in response to thyrotropin releasing hormone and not suppressed by glucose. The pituitary tumor partially resected by transsphenoidal surgery (TSS) was histologically diagnosed as pituitary adenoma. After surgery the basal levels of GH were decreased by about 60%, but both GH and IGF-1 levels remained elevated at about 20 ng/ml and 1000 ng/ml, respectively (Fig. 1, lower panel). In an attempt to reduce the GH levels, octreotide injection was begun immediately and the self-injection (300 µg/day) has been continued every day. After 4-year treatment with octreotide injection, the residual adenoma was markedly diminished and the basal GH level became lowerer to ~2 ng/ml (see Fig. 1). However, his cluster headache occurred even after adequate reduction of the volume of pituitary adenoma. His headache exhibited pulsatile pain and attacked him almost every morning; it lasted for 2 to 3 hours accompanied by occasional rhinorrhea or lacrimation. It was intriguing that the headache was relieved by octreotide injection but hardly reduced by common painkillers including anti-inflammatory and antimigraine drugs. After subcutaneous injection of octreotide (25 to 50 µg), his headache was ameliorated immediately within a few minutes, with the effects lasting for 2 to 6 hours after each injection. Successful treatment with octreotide was also shown in the metabolic normalization including glucose tolerance and serum lipid level. While his height and features remain almost unchanged, his body weight gain has stopped. There were no apparent side effects of octreotide including major gastrointestinal trouble and gallstones throughout the therapy.

Drug provocation test

In order to clarify the effectiveness of analgesic agents on the patient’s chronic headache, drug challenge tests were performed after obtaining informed consent. When the patient complained of severe headache, the analgesic effect of octreotide (25 µg s.c.), lidocaine (50 mg i.v.), morphine (3 mg i.v.) and thiopental (50–75 mg i.v.) was evaluated at our outpatient clinic. Each drug was administered following placebo
GIGANTISM TREATED WITH OCTREOTIDE

451

physiologic saline) injection and the pain intensity was evaluated using a 10-cm visual analogue scale (VAS) [3] before and 1 or 5 minutes after each injection. When the analgesic effect was incomplete, additive drug injections were subsequently performed and VAS was evaluated at 1 or 5 minutes after each injection. In case of the morphine test, a morphine antagonist, naloxone (0.2 mg i.v.), was administered after a series of morphine injections and the changes in VAS was reevaluated. As shown in Fig. 2, octreotide exhibited a remarkable analgesic effect and it completely suppressed the headache within 5 minutes. Lidocaine showed an unstable and slow effect with at most 40% reduction of the VAS score. Morphine rapidly reduced the VAS score to 56% of the placebo level, which was partially abolished by a subsequent administration of naloxone. Thiopental had no analgesic effect on his headache.

Discussion

Acromegaly/gigantism patients in general have some difficulties in handling the injections, resulting in its discontinuation. Nonetheless, a key factor that helped the present case to continue the self-injection regimen was the alleviative effect of octreotide on his headache that had been resistant to common painkillers. As reported in several cases of acromegaly [4–8], octreotide injection showed a potent and rapid effect that enabled our patient to reduce the magnitude of the cluster-like headache in a few minutes after injection.

The headache shown in acromegaly patients was associated with neither serum GH levels nor tumor size of pituitary adenoma as reported by Pascual et al. [9]. In the present case, the prompt and potent analgesic effect induced by octreotide was not mimicked by a sodium channel blocker lidocaine, which only marginally decreased the VAS of headache. Thiopental, a barbiturate, showed no effect on the VAS score in the present test, suggesting that the headache is not simply a psychogenic reaction. Thus, the characteristic of headache is, at least in part, opioid-sensitive since the opioid-receptor agonist morphine significantly reduced the VAS score, which was partially blocked by naloxone.

The analgesic mechanism of octreotide remains unclear. Octreotide is shown to bind to opioid receptors in vitro with a high affinity, by which octreotide exerts antagonistic properties to the opioids in animal studies [10]. On the contrary, Pascual and colleagues reported that the analgesic effect of octreotide was not influenced by the morphine antagonist naloxone, suggesting that mechanisms other than the opioid system may be involved in the analgesic effect of octreotide [9]. As the involvement of opioid receptor in the octreotide actions is controversial, future studies are necessary to elucidate the analgesic mechanism of octreotide in patients with acromegaly/gigantism, which would lead to clarifying the underlying mechanism of the intractable headache due to pituitary disorders.

It is possible that our patient could have developed octreotide dependency [11–13] regarding headache during the therapy. However, we must note that tachyphylaxis to octreotide did not emerge and that almost the same dose of octreotide has been effective to relieve the headache during the 4-year observation period, while the occurrence of octreotide tachyphylaxis on GH reduction has only rarely been reported in acromegaly [14–16]. Our present case hence shows the effectiveness of long-term treatment with octreotide on pituitary gigantism including GH reduction and tumor diminution as well as on headache control, the latter of which is highly likely to contribute to continuation of the self-injection regimen.
References