Original Article

Incidence of gall stone formation in acromegalic patients on octreotide therapy

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ABSTRACT

Objective: Octreotide, a long-acting synthetic somatostatin analog, has been widely used for ac-romegalic patients. Gastrointestinal (GI) side effects and gall stones are predominant side effects. We report incidence of gall stones in our cohort of acromegalic patients treated with octreotide therapy. **Design:** Retrospective case observational study. **Setting:** Endocrinology Unit, Dr. Ram Manohar Lohia, Hospital, New Delhi. **Materials and Methods:** Patients of acromegaly on primary or secondary octreotide therapy. **Intervention:** Patients were enquired regarding complaints related to the GI system and their medical records were reviewed. Ultrasound films at various intervals while on octerotide therapy were evaluated by the radiologist for presence of sludge and development of gall stones. **Results:** Of seven patients, five developed gallstones and sludge was seen in three patients at intervals ranging from 11 to 36 months postoctreotide initiation. **Conclusion:** A high incidence of gall stone formation in the present study as compared to the West was noted, the reasons for which are not clear.

Key words: Acromegaly, gall stones, octreotide

Introduction

Surgery is the primary modality of treatment in pituitary tumors characterized by GH excess. However, in about 20–40% of patients, GH levels remain high after surgery.[1] The use of dopamine agonists as an adjuvant medical therapy postsurgery has shown poor outcomes. Newer modalities of treatment such as somatostatin analogs and GHRH antagonist (pegvisomant) have shown encouraging results.

Octreotide, a long-acting synthetic somatostatin analog, has been widely used for acromegalic patients. Gastrointestinal (GI) side effects are the predominant complaints attributable to inhibition of GI and gall bladder motility and function.

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Gall stones have been reported in patients ranging from 11% to 34% in studies reported in the West.[2-4] To the best of our knowledge, there is no such previous report from India. We report here our experience on incidence on gall stones with octreotide therapy in acromegalic patients.

Materials and Methods

Patients with acromegaly who had received octreotide therapy for a period of at least 3 months were included in the study. All patients underwent detailed history and examination including their initial presenting complaints and present symptoms related to GIT while on octerotide therapy. Their medical records were reviewed for clinical, biochemical, hormonal details, and imaging. Ultrasound films at various intervals while on octerotide therapy were evaluated by the radiologist for presence of sludge and development of gall stones.

Results

There were seven patients, three males and four females, age ranging from 27 to 60 years. The initial presenting complaints included headache, visual disturbances,

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acromegalic features, and menstrual complaints. Two patients had diabetes mellitus, three were hypertensive, and one patient was hypothyroid, hypogonad, and hypocortisolemic at presentation. These patients had been symptomatic for a period ranging from 4 months to 4 years before diagnosis. Of seven patients, five had been on primary octerotide therapy, one received octreotide postsurgery, and one received octreotide postsurgery and gamma knife therapy. Postglucose GH and IGF1 levels before initiation of octreotide therapy ranged from 3.04 to 179 ng/ml and 361 to 1143 ng/ml, respectively.

These patients received octreotride therapy for a period ranging from 6 months to 13 months. All patients received monthly doses of 20 mg of long-acting octreotide (Octreotide LAR). Therapy was stopped and was restarted in three patients. Octreotride was well tolerated by all patients. IGF1 levels reduced to normal in all except three patients. There was no remission of the diabetic status in two patients with octreotide.

Table 1 shows the profile of GI symptoms in patients while on octreotide therapy. Table 2 shows the development of biliary sludge and gallstones in these patients.

Discussion

Octreotide is a long-acting synthetic somatostatin analog. It acts by binding to the somatostatin receptor subtypes 2 and 5, thereby decreasing the production growth hormone and IGF-1.[5] Octreotide is used as an adjuvant therapy to surgery and radiotherapy and is a preferred medical treatment in patients with acromegaly. Being a synthetic analog, its hydrolysis by the plasma peptidase is delayed which results in the desired prolonged duration of action. The drug is usually well tolerated; the most common side effects include diarrhea, abdominal discomfort, and nausea.[1] These side effects are usually self-limiting lasting for a period of upto 3 months after initiation of therapy.[6] Gall stone formation is frequent varying in prevalence from 11% to 34% in different studies.

There are a number of mechanisms contributing to the formation of gall stones, but none has been conclusively proven. Dowling laboratory were the pioneers of studies describing pathogenesis of the gall stone formation.[7] The bile in patients on octerotide is supersaturated in cholesterol resulting in cholesterol-rich gall stones.[8,9] Some studies have shown that such patients have impaired gall bladder contraction and prolonged small and large colonic reabsorption and transit, and increased proportion of deoxycholic acid in biliary bile acids.[9] Prolongation of large intestinal transit time causes increase in the number of fecal anaerobes and the activity of rate limiting enzyme pathway (7-α-dehydroxylation) which in turn increases the proportion of deoxycholic acid.[7] It is also believed that as a result of the slow colonic transit, there is an alteration of the pH of the colon making it more alkaline, thereby resulting in excess of soluble form of deoxycholic acid.[10] *De novo* synthesis of deoxycholic acid was also found to be increased in patients receiving octreotide by Bathgate *et al.*[2] Apart from the cholesterol supersaturation, octreotide administration is known to interfere with biliary tract motility due to inhibition of choleocystokinin release from the small intestine.[7,9] Additionally, octretotide administration inhibits the postprandial relaxation of the sphinter of Oddi.[4]

New gallstone formation has been reported in upto 34% of patients treated with depot somatostatin analogs.[2-4] Attansio *et al.* found that among 62 patients on LAN 60 (long acting somatostain analog) treatment, 12 had

Table 1: Profile of the patients related to gastrointestinal symptoms while on octeotride therapy

Initials of the patient	Bloating	Flatulence	Diarrhea/ Steatorrhea	Right upper quadrant pain
RKM	+	+	–	+
B	+	+	–	+
PD	+	+	+	+
YA	+	–	+	–
R	+	–	–	+
S	+	+	+	+
MA	+	+	+	–

All patients receiving octreotide complained of bloating. Flatulence was reported by 6 and diarrhea was reported by 4 patients. These symptoms were self-limiting in all, varying in durations ranging from 1 to 12 months. Five patients complained of right upper quadrant pain. Stool for occult blood was positive for none of the patients

Table 2: Shows the development of biliary sludge and gall stones in patients while on octreotide therapy

Initials of the patient	Biliary sludge	Interval post octreotide when first detected (months)	Gall bladder calculi	Interval postoctreotide when first detected (months)
RKM	+	11	Cholelithiasis	11
B	–	–	Cholelithiasis, showing multiple calculi.	12
PD	+	19	Cholelithiasis with gall bladder	36
YA	–		–	
R	–		Cholelithiasis	18
S	+	24	Multiple calculi present in the gall bladder	24
MA	–		–	

Of 7 patients, 5 developed gallstones and sludge was seen in 3 patients at intervals ranging from 11 to 36 months postoctreotide initiation

preexisting gallstones and 10 patients (11%) developed new biliary abnormalities (sludge or stones) while on treatment.[11] Catnach *et al.* reported gall stones in 34% of the 39 patients receiving octreotide.[12] However, another study reported a very high incidence of gallstones in six out of seven patients within 8 months of therapy.[13] Serial ultrasound scanning at 6-month interval for formation and progression of gall stones on somatostatin analogs was performed by Ayuk *et al.* They observed that in 4 of 22 subjects, gallstones developed 24–40 months after commencing treatment with long-acting somatostatin analogs and persisted throughout the study period, whereas in the remaining 1 subject gallstones were identified 2 months into the study period and steadily increased in number.[14] The gallbladder sludge was identified in 1 patient 34 months after commencing treatment and did not progress to gallstones during the study period (52 months).

In the present study, we observed GI side effects ranging from bloating and flatulence in all patients and diarrhoea in 57% of the patients. These complaints were self-limiting in all patients. In a study by Johan A Verhelst *et al.* on 66 patients, GI complaints were reported by 41 patients (62%).[15] Most prominent problems were diarrhoea, loose stools, abdominal cramps, and nausea, which were self-limiting. We observed gall stones in 71% of our patients. This proportion of gall stones prevalence is higher than that reported from the West (11–34%). Only one study by Moschetta *et al.* reported a very high incidence of gallstones in six of seven patients (85%) within 8 months of therapy.[13] Indian diet includes a higher proportion of carbohydrates and fats unlike the high-protein diet of the west. Gall bladder motility and function is proportional to the fat intake. It is possible that inhibition of gall bladder motility by octreotide in dynamic gall bladder as in Indians could cause a high proportion of gallstones.

In conclusion, we report a high incidence of gallstones with octreotide in acromegalic patients as compared to the western population. The reasons for this discrepancy are unclear.

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