Seizures in patients with idiopathic hypoparathyroidism: effect of antiepileptic drug withdrawal on recurrence of seizures and serum calcium control

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Abstract

Objective: There is limited information on seizures in patients with idiopathic hypoparathyroidism (IH). We assessed seizure characteristics at presentation, subclinical seizures during follow-up, and the effect of antiepileptic drug (AED) withdrawal in IH patients.

Designs and methods: Seizure characteristics were assessed in 70 patients with IH attending endocrine clinic. Provoked electroencephalography (EEG) was performed for subclinical seizures in 44 of them. AEDs were withdrawn using strict criteria, i.e. i) no seizure during past 2 years, ii) normal EEG, iii) serum total calcium ≥ 1.8 mmol/l, and iv) feasibility to follow-up regularly after AED withdrawal for at least 9 months ($n=14$). The effects of AED withdrawal on seizures and serum total calcium were assessed.

Results: Seizures were present in 64.3% of patients, generalized tonic-clonic in 86.7%, and treated with phenytoin (46.7%), valproate (40%), and carbamazepine (26.7%). Most (69/70) patients were seizure-free during the follow-up of 6.6 ± 4.5 years. Ten of 14 (71.4%) patients were successfully withdrawn from AED and remained seizure free during the follow-up period of 13.5 ± 2.4 months (range 9–18). AEDs were restarted because of the recurrence of seizures ($n=3$) and poor compliance with calcium/vitamin D ($n=1$). The mean serum total calcium increased from 1.9 ± 0.19 to 2.1 ± 0.14 mmol/l after AED withdrawal ($P=0.004$).

Conclusion: Seizures were present in 64.3% of patients with IH and they responded to AED and calcium/1- α -(OH)D during the follow-up. With strict eligibility criteria, it was possible to withdraw AED in 71% of patients with IH. Serum total calcium improved significantly after AED withdrawal.

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Introduction

Seizure is a common complaint in patients with idiopathic hypoparathyroidism (IH), occurring with a frequency of 60–70% (1, 2). Generalized tonic-clonic seizures (GTCS) are most common followed by petit mal, partial, atonic, and subclinical seizures assessed by electroencephalography (EEG) (1, 2, 3, 4, 5). Similar seizures are also observed in post-surgical IH with a

frequency of 18–31% (6, 7, 8). The general practice in the management of these patients is to supplement with calcium and vitamin D and to continue antiepileptic drugs (AED) for an undefined period. Though most patients respond to AED, there is a possibility of subclinical seizures despite treatment due to clinical practice of maintaining serum total calcium in low

normal range (NR). AED can have long-term adverse consequences including an effect on calcium homeostasis due to hepatic enzyme induction (9, 10).

There is limited information on seizure characteristics, possibly existing subclinical seizures on EEG during AED treatment and effect of AED withdrawal on recurrence of seizures and serum total calcium in IH. We have managed a large cohort of patients with IH since 1998 (11, 12, 13, 14, 15). In this study, we report our experience regarding management of seizures and effects of AED withdrawal in them.

Subjects and methods

Subjects were patients with IH attending the endocrine clinic of the All India Institute of Medical Sciences (AIIMS) during 2012–2014. Diagnosis of IH was based on the presence of hypocalcemia, hyperphosphatemia, low or inappropriately normal serum intact PTH (iPTH), and normal serum creatinine and magnesium (11, 12, 13, 14, 15). Information on calcium sensing receptor (CaSR), NALP5 autoantibodies, and selective genetic mutations was available in a subset of the study subjects ($n=58$) as reported earlier (15). CaSRAb was present in 11 (19.0%). None of them had NALP5Ab and *PTH* gene mutation, and *GCMB* (*GCM2*) and *CASR* gene mutations were present in only two and one of them respectively. Two of them had APECED syndrome.

Patients were managed with daily supplementation of two to four tablets of calcium carbonate (each containing 500 mg of elemental calcium and 250 IU of cholecalciferol) and 0.5–2.0 µg of 1- α -(OH)D. They were followed up regularly with an aim to maintain serum total calcium in the range of 2.0–2.1 mmol/l. Patients were investigated documenting details of seizures, EEG abnormalities at initial evaluation of seizures, and AED used. The subjects with neurological illness and fractures were excluded. Provoked EEG was performed to assess the presence of subclinical seizures. AED were withdrawn in selected patients. The procedure for provoked EEG, eligibility criteria, and protocol for AED withdrawal and the assessment of its effects on recurrence of seizures and serum total calcium are described below.

Assessment of subclinical seizures

Subclinical seizures were assessed by provoked EEG following sleep deprivation, photic stimulation, and hyperventilation. Patients were admitted a night before the pre-appointed date of EEG in the endocrine unit for

ensuring sleep deprivation under supervision. They were advised to remain awake by engaging themselves in reading, listening to music, and chatting with attendants, but to abstain from stimulants such as tea, coffee, tobacco, or smoking and to sleep only during 0000–0300 h. A blood sample was drawn in the fasting state at 0800 h for serum total calcium, inorganic phosphorus, serum alkaline phosphatase (SAP), albumin, and 25(OH)D. A light breakfast and morning dose of AED, calcium, and vitamin D were permitted and surface EEG was performed at 0900 h (16 channels with 10–20 system of electrodes, XLTEK, Natus Medical, Inc., San Carlos, CA, USA). Photic stimulation was provided by a flickering light flashed for 5 s followed by 5 s of pause. The frequency of light was successively increased from 1 to 30 Hz. During hyperventilation, patients were asked to take deep breaths at a rate of 20/min for 4 min. After the provoked EEG, they were asked to relax and sleep for EEG recording during sleep.

Eligibility criteria and protocol for withdrawal of AED

The criteria for AED withdrawal were as per American Association of Neurology guidelines for patients with epilepsy, i.e. i) normal EEG before AED withdrawal and ii) no overt seizures during the past 2 years (16). Besides, average serum total calcium concentration of ≥ 1.8 mmol/l in the last three visits was an additional criterion to prevent hypocalcemic seizures. The AEDs were withdrawn as per the general clinical practice in the management of epilepsy. Sequential withdrawal was performed in patients on multiple AED. The drug started first was withdrawn first. Dose of AED was reduced by 25% every month. Serum levels of total calcium, inorganic phosphorus, SAP, and 25(OH)D were measured on each visit. The patients were advised to maintain the prescribed dose of calcium and 1- α -(OH)D, dietary habits, exercise schedule, and were provided telephonic contact of the authors (S Modi and R Goswami) for emergency advice. Out-station patients were excluded due to nonfeasibility of monthly follow-up.

Assessment of the effects of AED withdrawal on seizures and calcium homeostasis

After complete cessation of AED, patients were followed up monthly for 3 months and every 3 months thereafter for a total duration of at least 9 months. Serum total calcium, inorganic phosphorus, and SAP were measured at each visit. Calcium and 1- α -(OH)D were

continued in the same dose and compliance was facilitated by providing it free of cost to non-affording patients. Repeat EEG was performed a month after complete withdrawal of AED. Effect of AED withdrawal on serum total calcium was assessed by comparing pre- and post-withdrawal values. The average of three serum calcium values measured at least one week apart prior to initiation of AED withdrawal was taken as the pre-withdrawal value. The average of serum total calcium drawn after complete AED withdrawal till the last follow-up was taken as the post-withdrawal value. The study protocol was approved by the Institutional Ethical Committee of the AIIMS.

Biochemical assessment

Serum levels of total calcium, inorganic phosphorus, and SAP were measured using standard laboratory procedures, with an automated analyser (Modular P 800, Roche/Hitachi; NR: 2.0–2.6, 0.8–1.5 mmol/l, and 80–240 IU/l respectively) with intra- and interassay coefficients of variation of 3.5–5.0%. Serum 25(OH)D was measured by chemiluminescence (LIAISON 25(OH)D total assay; DiaSorin, Inc., Stillwater, MN, USA) and serum intact parathyroid hormone (iPTH) by IRMA till 2006 (DiaSorin, minimum detection, 0.7 ng/l and NR, 13–54 ng/l) and afterwards by electrochemiluminescence (Elecsys-2010, Roche; NR: 15–65 ng/l) in the endocrine service laboratory as described earlier (13, 14).

Statistical analysis

Data are shown as mean and s.d. with frequencies in percentage. The clinical and biochemical characteristics of patients with and without seizures were compared by parametric and nonparametric tests as appropriate. The data were analysed using SPSS (version 11.5) and P value <0.05 was considered significant.

Results

Seventy-five patients with IH attended endocrine clinic during the study period (Fig. 1). Five were excluded because of head injury, stroke, acoustic schwannoma, vasculitis, and vertebral fractures (one each). The mean age and male:female ratio for the 70 subjects were 36.8 ± 14.89 years and 33:37 respectively. Seizures were present in 45 (64.3%) and were the initial complaint in 29 (41.4%). The mean duration between the onset of seizures and diagnosis of IH was 6.9 ± 5.72 years. At presentation,

Figure 1

Flow of the patients in the study.

patients with seizures were younger (27.3 ± 12.9 vs 34.8 ± 11.6 years, $P=0.02$), had higher mean serum phosphorus (2.4 ± 0.47 vs 2.0 ± 0.33 mmol/l, $P=0.001$), and higher frequency of basal ganglia calcification (91.1 vs 56.0% , $P<0.002$) compared with those without seizures. However, the gender ratio, frequency of cataract, mean serum total calcium level, 24-h urinary calcium excretion, and iPTH were comparable in two groups (Table 1). EEG during initial evaluation of seizures was available in 12 of the 45 patients and showed diffuse slow-wave activity in four; left temporal epileptiform discharges, intermittent 'sharp and slow waves', and transient generalized poly-spikes in one each. EEG was normal in five.

Seizure characteristics and AED used

Among 45 patients with seizures, 39 (86.7%) had GTCS and two (4.4%) had left complex partial seizures. The characteristics of seizures could not be ascertained in four (8.9%). The frequency of seizures was at least once a day in eight (17.8%) and less than once daily to once a month in nine

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Table 1 Clinical and biochemical characteristics (means and s.d.) in hypoparathyroidism patients presenting with and without seizures. Normal range: serum total calcium, 2.0–2.6 mmol/l; serum inorganic phosphorus, 0.8–1.5 mmol/l; and iPTH, 15–65 ng/l.

Parameters	History of seizures		P
	Present (n=45)	Absent (n=25)	
Sex (M:F)	25:20	8:17	0.081
Age at onset of symptoms (years)	20.7 ± 13.99	28.0 ± 12.01	0.031
Age at initial presentation (years)	27.3 ± 12.89	34.8 ± 11.63	0.02
Duration of illness at initial presentation (years)	6.9 ± 5.72	6.7 ± 5.13	0.92
Current duration of illness (years)	12.7 ± 7.56	14.9 ± 6.52	0.22
Basal ganglia calcification (%)	91.1	56	0.002
Cataract (%)	48.8	36	0.44
Serum total Ca at initial presentation (mmol/l)	1.4 ± 0.25	1.4 ± 0.28	0.26
Serum PO ₄ at initial presentation (mmol/l)	2.4 ± 0.47	2.0 ± 0.33	0.001
24-h urinary calcium excretion at initial presentation (mmol/day)	1.9 ± 1.24	2.1 ± 1.34	0.63
Serum iPTH at initial presentation (ng/l)	7.8 ± 7.45	10.6 ± 12.11	0.24

(20%). Among 12 (26.7%) patients, seizures occurred with lesser frequency, and in six (13.3%) there was only one episode before presentation. Details of seizure frequency could not be elicited by ten (22.25%) patients. Eleven of the 45 (24.4%) patients had poor response to AED before the diagnosis of IH and initiation of calcium and vitamin D therapy. Seizures were managed by one AED in 71%, by two in 20%, and by three in 8.9% of the patients. The AED used and their frequency were phenytoin (46.7%), valproate (40%), carbamazepine (26.7%), levetiracetam (13.3%), clobazam (8.9%), and phenobarbitone (2.2%).

Overt and subclinical seizures on AED therapy

The mean serum total calcium, phosphorus, and 24-h urinary calcium excretion during follow-up in patients with and without history of seizures were comparable (1.8 ± 0.19 vs 1.8 ± 0.14 mmol/l, $P=0.73$; 2.0 ± 0.33 vs 1.8 ± 0.25 mmol/l, $P=0.10$; and 3.5 ± 3.15 vs 3.2 ± 1.45 mmol/day, $P=0.66$ respectively). All patients in both the groups were free from overt seizures during the follow-up of 6.6 ± 4.5 years, except one. This patient, a 17-year-old male with history of recurrent seizures since 10 years of age was recently recruited in our cohort. Provoked EEG was performed in 44 consenting patients (31 with and 13 without history of seizures) and was normal in all of them. Among 31 patients, 22 with seizures were on AED during the study.

Effect of AED withdrawal on the recurrence of seizures

Fourteen of the 22 patients receiving AED fulfilled the withdrawal criteria. Ten of them could complete the

AED withdrawal and were seizure free till the last follow-up without AED at a mean interval of 13.5 ± 2.4 months (range 9–18 months). Repeat provoked EEG was normal in all patients; however, in one patient, despite no recurrence of seizure, a clinical decision was made to restart AED at 6 months of follow-up because of poor compliance to calcium and vitamin D therapy. Three patients had recurrence of seizures and their details are as follow:

Case 1 ► A 28-year-old female had recurrent GTCS since 14 years of age. She was diagnosed to have IH 8 years back and had no seizures on daily calcium, 1- α -(OH)D, and phenytoin (200 mg/day). During the second month of AED withdrawal, her phenytoin dose was reduced to 100 mg. Two days later she developed twitching of face and eyelids occurring six to eight times per day. Her serum total calcium and 25OHD levels were 2.1 mmol/l and 110 nmol/l respectively. EEG was normal and seizures responded with increase in phenytoin to 200 mg.

Case 2 ► A 28-year-old male had recurrent GTCS since the age of 14 years with partial response to phenytoin. One year later, he was diagnosed with IH and treated with calcium and 1- α -(OH)D. There were no seizures during 13 years of follow-up. Five months after AED withdrawal, he had GTCS. History revealed poor compliance with calcium and vitamin D therapy, lack of sleep, and stress due to demise of his grandfather. His serum total calcium was 1.4 mmol/l. Serum 25OHD was normal (92.5 nmol/l). He was counseled for regular calcium and vitamin D therapy and phenytoin was restarted.

Case 3 ► A 36-year-old male, had multiple GTCS since the age of 10 years and was hospitalized with status epilepticus 4 years back. Despite phenytoin and valproate therapy, subclinical seizures persisted and on evaluation IH was diagnosed. EEG abnormalities subsided with i.v. calcium gluconate and oral calcium and 1- α -(OH)D were added to AED therapy. Phenytoin was stopped after 4 months and during the next 3 years he was seizure free on valproate. Two months after complete AED withdrawal he had GTCS. Serum total calcium and 25OHD were 1.6 and 125 nmol/l respectively. History revealed missed doses of 1- α -(OH)D due to nonavailability at local market. On the day of seizure, he was also stressed due to a theft at his office. He was counseled and put back on valproate.

To assess the relationship of recurrence of seizures with intracranial calcifications, sites of calcification were compared between patients with and without recurrence of seizures. Nine of the 11 patients with no recurrence of seizures had basal ganglia calcification. Seven of them had associated calcification at gray-white junction (subcortical) and at deep white matter (also referred as centrum semiovale) and their frequencies were as follows: frontal subcortical ($n=2$), frontal and parietal subcortical ($n=1$), fronto-parieto-temporal subcortical and deep white matter ($n=1$), and deep white matter ($n=3$). One of the 11 had only deep white matter calcification. All three patients with recurrence of seizures had basal ganglia and other intracranial calcifications (frontal subcortical ($n=1$), parieto-temporo-occipital subcortical, and deep white matter ($n=1$)). Computed tomography (CT) film was not available in one of them. However, the CT report

mentioned the presence of subcortical and deep white matter calcification.

Effect of AED withdrawal on calcium homeostasis

Mean serum total calcium concentration significantly improved after successful AED withdrawal (pre-withdrawal, 1.9 ± 0.19 – 2.1 ± 0.14 mmol/l; $P=0.004$). In six patients, it reached the target range of 2.0–2.1 mmol/l with ongoing dose of calcium and 1- α -(OH)D (Fig. 2). There was no change in the mean serum phosphorus (1.8 ± 0.35 vs 1.7 ± 0.28 mmol/l, $P=0.15$), SAP (358 ± 303 vs 281 ± 184 IU/l, $P=0.13$), serum 25(OH)D (76.1 ± 15.48 vs 86.6 ± 17.02 nmol/l, $P=0.06$), and 24-h urinary calcium (2.8 ± 1.39 vs 3.9 ± 1.64 mmol, $P=0.10$) after AED withdrawal.

Discussion

The present study revealed 64% prevalence of seizures in patients with IH. These were the presenting complaints in 41%. Despite clinically overt GTCS, which were refractory to AED in one-fourth, the diagnosis of IH was delayed by several years. This suggests a need for higher awareness among medical personnel to include serum total calcium and inorganic phosphorus measurement in the diagnostic workup of seizures.

Diffuse slow-wave activity was the characteristic EEG finding at the initial evaluation of seizures and has been described earlier (4, 5, 17, 18). The association of intracranial calcification with seizures has also been reported in our earlier study (13). Interestingly, we observed that patients with seizures had significantly lower age at the onset of symptoms than those without seizures despite comparable mean serum calcium at presentation. This could be a reflection of generally increased predisposition of children to seizures (19).

During long-term follow-up, none of the patients with or without AED had recurrence or onset of new seizures on calcium and vitamin D therapy at mean serum calcium value of 1.8 mmol/l. Similarly, though their average serum calcium concentration was 1.8 mmol/l on the day of provoked EEG, none showed any epileptiform activity. This indicated that patients with IH may not be at risk of seizures if their serum calcium concentration is maintained at 1.8 mmol/l or above. There is no information on EEG activity in a large cohort of patients with IH in a long-term follow-up. Odoriz *et al.* (4) assessed EEG abnormalities in 17 patients with hypoparathyroidism and showed

Figure 2

Change in serum total calcium concentration after withdrawal of antiepileptic drug in patients with idiopathic hypoparathyroidism.

its normalization with a gradual improvement in serum total calcium concentration.

There are no data on the effect of AED withdrawal on the recurrence of seizures in patients with IH. In the present study, 71% could be successfully withdrawn from the AED. The factors precipitating recurrence of seizures were emotional stress, sleep deprivation, and poor compliance with calcium and vitamin D therapy. The recurrence rate for seizures and precipitating factors were similar to that reported for non-hypoparathyroid epilepsy (20, 21). Berg & Shinnar (20) observed 25% recurrence rate during the first year of AED withdrawal in epilepsy. A recent study in patients with epilepsy has reported noncompliance with medications (40.9%), emotional stress (31.3%), sleep deprivation (19.7%), and fatigue (15.3%) as the common factors triggering seizures (21).

Despite usefulness of AED in the management of seizures, their adverse effect on calcium homeostasis has been of concern. These drugs can affect vitamin D metabolism and inhibit intestinal calcium absorption (9, 10, 22). The effect of these drugs and their withdrawal on serum total calcium in patients with IH has not been reported earlier. In the present study, phenytoin, valproate, and carbamazepine were the most commonly used AED and their withdrawal led to significant improvement in the serum total calcium. Several patients could achieve the target serum total calcium concentration of 2.0–2.1 mmol/l which was not achieved while they were on AED. The improvement in serum calcium was not associated with reduction in urinary calcium excretion. Further studies assessing serum 1,25(OH)₂D would be helpful to understand the mechanism of improved serum total calcium after AED withdrawal in IH.

To conclude, clinically overt seizures were present in two-third of patients with IH. They responded adequately to AED and calcium and 1- α -(OH)D therapy with no overt or subclinical seizures during follow-up. Withdrawal of AED was successful in 71% of the cases, selected using strict withdrawal criteria, and led to improvement in serum total calcium. Thus, under careful supervision, AED withdrawal might be attempted in eligible patients with IH.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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