CASE REPORT
Adult onset recurrent seizures as the first presentation of primary hypoparathyroidism [version 1; referees: 2 approved with reservations]

Pamela Correia, Rajeev Ranjan, Chandrashekhar Agrawal
Department of Neurology, Sir Ganga Ram Hospital, New Delhi, India

Abstract
Introduction: Hypoparathyroidism leading to hypocalcemia is an important treatable cause of recurrent seizures. Primary hypoparathyroidism presenting for the first time as seizures in adulthood is quite infrequent. Patients may present with hypocalcemic seizures even in the absence of subtle hypocalcemic signs.

Case report: A 30 year old male, was presented to the emergency facility in an unconscious condition. He was intubated on the way to the hospital as he had suffered from two episodes of ventricular tachycardia. He had previous history of recurrent seizures for 6 years inspite of multiple anticonvulsants including phenytoin sodium, sodium valproate, and levetiracetam. The seizure frequency increased in the last year and he would have 5-6 episodes/month. A MRI brain scan and EEG at the onset were both normal, as was the general examination but he had history of bilateral cataracts. There were no signs of tetany. Investigations revealed a normal hemoglobin and glucose level with normal electrolytes and both TLC and DLC levels were also normal. He had a serum calcium level of 3.3 mg% with a serum parathyroid hormone level of 1pg/ml, serum 25(OH) vitamin D levels of 6.6ng/ml and hypomagnesemia. NCCT head scan showed bilateral basal ganglia, and deep white matter calcification.

Conclusions: 1) Ironically, increasing reliance on high end investigations such as a MRI brain scan could lead to certain conditions being missed; conditions that could be easily identifiable by the humble CT scan. 2) All treatable metabolic conditions should be excluded at first before commencing with anticonvulsants; this will restrict patients from burdensome polytherapy and related side effects.

Corresponding author: Pamela Correia (pamela983in@yahoo.co.in)
How to cite this article: Correia P, Ranjan R and Agrawal C. Adult onset recurrent seizures as the first presentation of primary hypoparathyroidism [version 1; referees: 2 approved with reservations] F1000Research 2012, 1:51 (doi: 10.12688/f1000research.1-51.v1)
Copyright: © 2012 Correia P et al. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).
Grant information: The author(s) declared that no grants were involved in supporting this work.
Competing interests: No competing interests were disclosed.
Introduction
Hypoparathyroidism leading to hypocalcemia is an important treatable cause of recurrent seizures. Even though it is not an uncommon condition, primary hypoparathyroidism presenting for the first time as seizures in adulthood is quite infrequent. Patients may present with hypocalcemic seizures even in the absence of subtle hypocalcemic signs inclusive of tetany, Chvostek’s sign or carpopedal spasms. As this is an entirely treatable condition, a high index of suspicion for primary hypoparathyroidism with hypocalcemic seizures should be maintained even in otherwise asymptomatic adults.

Case report
A 30 year old male, was presented to the emergency facility in an unconscious condition. He had been intubated on the way to the hospital as he had suffered from two episodes of ventricular tachycardia in the cardiac ambulance. He was being transported from a local hospital where he had been admitted for profuse diarrhea with dehydration.

He recovered during the hospital stay and on further inquiry it was discovered that he had a past history of recurrent seizures for the last 6 years in spite of being on multiple antiepileptic medications including phenytoin sodium, sodium valproate and leviteracitam. The seizure frequency had increased considerably in the last year, and he would have at least 5–6 episodes in a month, thereby creating a considerable toll on his personal and professional life. He had been evaluated with an MRI brain scan and an EEG at the onset of symptoms 6 years earlier and both were reported to be normal.

General physical examination was relatively normal, though he had a past history of being operated for bilateral cataracts six months ago. Also fundoscopic examination showed bilateral acute papillodema. There was no carpopedal spasm or any other signs of tetany like Chvostek’s or Trousseau’s sign.

Investigations revealed normal hemoglobin and glucose level with normal sodium and potassium levels. TLC and DLC levels were also normal. He was found to have a serum calcium level of 3.3 mg% with a serum parathyroid hormone level of 1 pg/ml, serum 25(OH) vitamin D levels of 6.6 ng/ml and hypomagnesemia. NCCT head scan was done which showed bilateral basal ganglia calcification and deep white matter calcification. A 2D ECHO study was performed, and showed normal results (Figures 1 and 2).

Discussion
Intracranial calcifications can be classified mainly into 6 groups based on their etiopathogenesis: age-related and physiologic, congenital, infectious, endocrine and metabolic, vascular, and neoplastic1 (Table 1). The function of the parathyroid hormone is primarily maintaining the plasma calcium levels. Hormonal disturbance of...
the parathyroid glands including hypoparathyroidism, hyperparathyroidism and pseudohypoparathyroidism may lead to intracranial calcifications. Calcium accumulation is demonstrated primarily in the bilateral basal ganglia, dentate nuclei, and peripheral subcortical white matter sites.

The principal function of the parathyroid hormone (PTH) is the maintenance of calcium plasmatic levels, withdrawing the calcium from bone tissue, reabsorbing it from the glomerular filtrate, and indirectly increasing its intestinal absorption by stimulating active vitamin D (calcitriol) production. There are two mechanisms that may alter its function, limiting its control on calcium: 1) insufficient PTH production by the parathyroids (hypoparathyroidism), or 2) resistance against its action in target tissues (pseudohypoparathyroidism). In both cases, there are significantly reduced levels of 1.25(OH) 2D and the alkaline phosphatase level.

Table 1. Causes of intracranial calcifications.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-related and physiologic</td>
<td>Pineal gland, habenula, choroid plexus, falx cerebri, tentorium cerebelli, dura mater, petroclinoïd ligament, sagittal sinus</td>
</tr>
<tr>
<td>Congenital</td>
<td>Sturge-Weber syndrome, tuberous sclerosis, neurofibromatosis, lipoma, Cockayne syndrome, Gorlin syndrome</td>
</tr>
<tr>
<td>Infectious</td>
<td>TORCH diseases, granulomatous infections, chronic viral encephalitis</td>
</tr>
<tr>
<td>Endocrine &amp; Metabolic</td>
<td>Fahr disease, hypothyroidism, hyperparathyroidism, pseudohypoparathyroidism, postthyroidectomy</td>
</tr>
<tr>
<td>Vascular</td>
<td>Primary atherosclerosis, cavernous malformation, arteriovenous malformation, aneurysms, dystrophic in chronic infarction and chronic vasculitis</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Oligodendroglioma, craniopharyngioma, germ cell neoplasms, neurocytoma, primitive neuroectodermal tumor (PNET), ependymoma, ganglioglioma, dyssembryonic neuroectodermal tumor (DNET), meningioma, choroid plexus papilloma, medulloblastoma, low grade astrocytoma, pilocytic astrocytoma, pinealoma, pinealoblastoma, schwannoma, dermoid, epidermoid, calcified metastases (osteogenic sarcoma, mucinous adenocarcinoma)</td>
</tr>
</tbody>
</table>

In acute and/or severe symptomatic hypocalcemia there is a predominance of neuromuscular, neuropsychiatric, and cardiovascular abnormalities. There is an increase in neuromuscular excitability, latent or evident, with sensory and motor disruption. Perioral or extremity paresthesia, cramps, myalgia, and muscular weakness are mild to moderate symptoms. Neuropsychiatric manifestations include irritability, anxiety, psychosis, hallucinations, dementia, depression, mental confusion, and extrapyramidal abnormalities. Increased intracranial pressure, papilledema, and convulsions can also be present, and must be differentiated from severe tetany muscular spasms. Typical clinical signs of neuromuscular irritability associated with latent tetany include hyperreflexia and Chvostek’s and Trouseau’s signs, respectively. Severe hypocalcemia may result in bradycardia or ventricular arrhythmias, cardiovascular collapse, and hypotension that is non-responsive to fluids and vasopressors.

A decrease in myocardial contractility occurs, as well as a typical electrocardiographic abnormality, which is the rate-corrected QT interval (QTc) prolongation. Patients with chronic hypocalcemia may or may not have symptoms of discreet neuromuscular irritation, even with markedly low calcium levels. Asymptomatic cases may be detected by chance, by the dosage of calcium in routine exams, during periods of greater calcium demand (i.e. gestation, lactation, menstrual cycle and states of alkalosis), or during the use of hypocalcemic drugs (i.e. bisphosphonates).

Significant cognitive deficits, neuropsychiatric abnormalities, and extrapyramidal symptoms that resemble Parkinson’s disease or chorea are associated with the calcification of basal ganglia, which occurs in all forms of chronic hypocalcemia and may be detected with greater sensibility using computerized tomography. Other findings of chronic hypocalcemia include sub-capsular cataracts, an increase in bone mineral density (BMD), and greater susceptibility to dystonic reactions induced by phenothiazines.

Differential diagnosis of hypocalcemia will depend largely upon PTH and phosphorus levels, evaluated along with other clinical and laboratory data (Table 1). Cases presenting hypophosphatemia should include differential diagnosis of vitamin D, while cases associated with hyperphosphatemia are determined according to PTH levels. Hypoparathyroidism is an abnormality caused by a parathyroid hormone (PTH) secretion deficiency, and encompasses heterogeneous conditions (Table 2), which makes etiological differentiation crucial to the detection of abnormalities associated with some of these diseases beforehand, thereby preventing complications. Signs and symptoms are caused by hypocalcemia.

Laboratory measurements present hypocalcemia, hyperphosphatemia, and inappropriately low or undetectable PTH. Generally, levels of 1.25(OH) 2D are low and the alkaline phosphatase level

Table 2. Causes of hypoparathyroidism.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid Destruction</td>
<td>Surgery</td>
</tr>
<tr>
<td>Auto-immune (isolated or polyglandular)</td>
<td>Cervical irradiation</td>
</tr>
<tr>
<td>Infiltration by metastasis or systemic diseases (Sarcoidosis, amyloidosis, hemochromatosis, Wilson's disease, thalassemia)</td>
<td></td>
</tr>
<tr>
<td>Reduced parathyroid function</td>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>PTH gene defects</td>
<td>Calcium sensing receptor mutations</td>
</tr>
<tr>
<td>Parathyroid agenesis</td>
<td>DiGeorge Syndrome</td>
</tr>
<tr>
<td>Isolated x-linked hypoparathyroidism</td>
<td>Kenny-Caffey syndrome</td>
</tr>
<tr>
<td>Mitochondrial neuropathies</td>
<td></td>
</tr>
</tbody>
</table>
is normal. In the majority of cases, hypoparathyroidism is sporadic, but there are familial cases in which transmission may be autosomic recessive, dominant, or X-linked.

Management of acute or severe symptomatic hypocalcemia must be made with intravenous calcium, with the goal of interrupting symptoms, preventing laryngeal spasm, and maintain total calcium levels above 7.0–7.5 mg/dL (ionized calcium greater than 0.7 mmol/L). Long-term treatment of patients with chronic hypocalcemia is done with 1 to 3 grams of elemental calcium per day in the various forms of salts available.

All patients with hypoparathyroidism or pseudohypoparathyroidism who become hypocalcemic must use vitamin D or analogues in addition to calcium. The vast majority of patients obtain control with calcitriol in dosages of 0.25 μg, taken twice daily, up to 0.5 μg four times daily. Hypoparathyroidism causes increased excretion of urinary calcium in relation to serum calcium and predisposes hypercalciuria, nephrolithiasis, and nephrocalcinosis. The product of calcium × phosphate must be kept below 55. Patients must have their kidneys radiologically evaluated regularly in order to rule out nephrocalcinosis.

Conclusion
1. Ironically, increasing reliance on high end investigations such as a MRI brain scan could lead to certain conditions being missed; conditions that could be easily identifiable by the humble CT scan.

2. All treatable metabolic conditions should be excluded at first before commencing with anticonvulsants; this will restrict patients from burdensome polytherapy and related side effects.

Consent
Written consent was obtained for publication of the patient’s clinical details and images obtained from the patient.

Author contributions
PC compiled the entire dataset and wrote the entire report. RR was a treating neurophysician for the work and overlooked the writing of the report and CSA contributed to the data collection and report writing.

Competing interests
No competing interests were disclosed.

Grant information
The author(s) declared that no grants were involved in supporting this work.

Acknowledgements
We would like to thank the Department of Endocrinology & Radiology for their support in the diagnosis of the patient at Sir Ganga Ram Hospital, New Delhi, India.

References
Open Peer Review

Current Referee Status: ?  ?

Version 1

Referee Report 08 February 2013

doi:10.5256/f1000research.227.r370

Michael A Levine
Division of Endocrinology and Diabetes, Center for Bone Health, The Childrens Hospital of Philadelphia, Philadelphia, PA, USA

I do not believe that this case report advances this field as such findings are quite trivial. The tables are incorrect or incomplete and omits GCM2 mutations as a cause of hypoparathyroidism.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Referee Report 21 November 2012

doi:10.5256/f1000research.227.r367

Gordon Klein
Children's Hospital, University of Texas Medical Branch at Galveston, Galveston, TX, USA

A few comments should be made about this case report. The first is that the authors note low serum levels of 25 hydroxyvitamin D. This is not parathyroid hormone (PTH) dependent and an etiology should be sought, i.e. inadequate sun exposure or failure of adequate vitamin D in the diet or any dietary supplements. Also, the low serum magnesium levels, while not reported, might contribute to peripheral PTH resistance.

Another thing to note is that advances in this field should be anticipated. For example, the use of parathyroid hormone replacement therapy and the advent of calcilytics (which are not yet marketed), would interfere with the action of the parathyroid calcium sensing receptor preventing a decrease in the set point for circulating calcium suppression of parathyroid hormone production or release.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.