# Fahr´s Syndrome; Pseudohypoparathyroidism Type Ib Masquerading as Epileptic Seizures

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## ABSTRACT

Hypocalcaemia of various origin can be manifested by paresthesia, muscle cramps, muscle weakness, syncope, convulsions and even severe psychomotor retardation. Such symptoms can be initially considered as signs of epilepsy. We present a 12-year old boy with partial seizures and basal ganglia calcifications, initially diagnosed as having Fahr´s disease and epilepsy, where severe hypocalcaemia, due to genetically confirmed pseudohypoparathyroidism type Ib was the underlying cause. Excellent clinical improvement was observed after calcium and vitamin D therapy. The basal ganglia calcifications were secondary due to chronic hypocalcaemia, therefore the appropriate diagnosis was pseudohypoparathyroidism type Ib with Fahr´s syndrome, but not Fahr´s disease. In conclusion, the serum evaluation of minerals, especially calcium and phosphate, should be performed in all patients with convulsions, cramps and psychomotor retardation. This is essential in arriving at a proper diagnosis and early initiation of appropriate treatment.

## KEY WORDS

*Calcium, Convulsions, Fahr´s syndrome, Hypocalcaemia, Intracerebral calcifications, Pseudohypoparathyroidism*

## INTRODUCTION

Mineral metabolism disorders, in particular hypocalcaemia, can result in various clinical manifestations, such as neuromuscular dysfunction, paresthesia, muscle cramps, muscle weakness, syncope, convulsions and in case of chronic hypocalcaemia even severe psychomotor retardation.[1-6] These symptoms can be initially considered as signs of epilepsy.[4-9] In known epilepsy, hypocalcaemia lowers the threshold for seizure activity.[1-4] We present a paediatric patient, initially diagnosed as having epilepsy, where severe hypocalcaemia, due to pseudohypoparathyroidism (PHP) was the underlying cause.

## CASE REPORT

A 12-year old boy was referred to paediatric neurologist because of partial seizures with a complex symptomatology. The patient had a complicated personal history, as he was delivered on 31st gestational week by a Caesarean section because of breech presentation and abnormal fetal heart rate. His birthweight was 1400 g, birthlength 43 cm and was treated at the neonatal intensive care unit. During infancy he underwent surgical correction of umbilical hernia and hydrocele, operation of medial cervical fistula at the age of two years and adenotomy at the age of three years, respectively. At the age of four years he suffered a single attack of simple febrile seizures. Electroencephalography (EEG) was normal, while magnetic resonance imaging (MRI) of the brain performed at that time was suggestive of Arnold-Chiari malformation. At nine years he also underwent ophthalmologic corrective operation of hypermetropy and strabism. At the pre-school age he was diagnosed as having bronchial asthma, this however resolved spontaneously before the age of ten years. There was also a mild psychomotor retardation.

At the age of 12 years his parents observed a brief episode, lasting for approximately one minute, when he was restlessly walking at home, and did not react to parents´ questions. This was also accompanied by wheezing and hypersalivation together with unability to speak, all

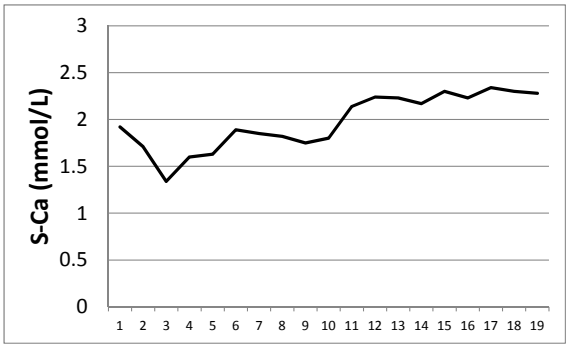


**Figure 1.** **Total calcemia (S-Ca; mmol/L) on a monthly basis (reference values 2.2-2.7 mmol/L)**

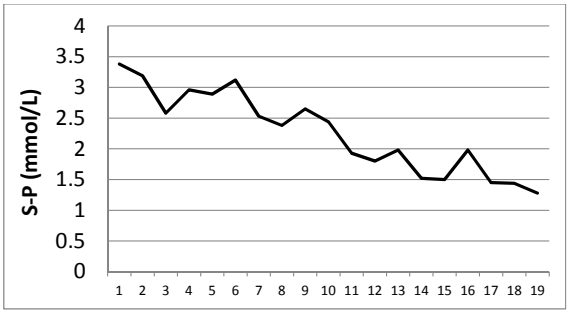


**Figure 2.** **Serum phosphate levels (S-P; mmol/L) on a monthly basis (reference values 0.6-1.6 mmol/L)**

followed by retrograde amnesia. The parents later recalled a similar situation that occurred three months earlier. Upon initial examination he was clumsy and manifested slowness of mental reactions with dyslalia and bradylalia, together with perioral twitching. He had positive Chvostek´s sign and apparent muscle weakness. His body height was 152 cm (-0.4 SD), body weight 47 kg (+0.5 SD), body mass index (BMI) 20.4 (+0.7 SD). He had no dysmorfic features, his external genitalia were of normal development according to age, blood pressure was 112/67 mmHg. Electroencephalography (EEG) was abnormal with specific sharp graphoelements and spikes, in particular high delta waves and theta waves, interpreted as epileptiform brain activity by the consultant neurologist. On electromyography (EMG) signs of latent tetany were apparent. Brain MRI revealed hyperintensities and bilateral symmetrical calcifications of the basal ganglia, and of thalamus and nucleus dentatus with otherwise normal central nervous system anatomy. Arnold-Chiari malformation was not confirmed. Furthermore, his laboratory results showed normal blood count, normal serum levels of glucose, sodium, potassium, iron, urea nitrogen, creatinine, bilirubin, alanin-aminotransferase, aspartate-aminotransferase and alkaline phosphatase (S-ALP), together with normal free thyroxine and thyrotropin. However, his total serum calcium was low (S-Ca 1.92 mmol/L; normal 2.2-2.7 mmol/L) (Fig. 1), ionized calcium level (S-Ca2+) was correspondingly low (0.9 mmol/L; normal 1.12–1.23 mmol/L), serum magnesium (S-Mg) was 0.9 mmol/L (normal 0.7–1.1 mmol/L) and serum phosphate level was high (S-P 3.38 mmol/L; normal 0.6-1.6 mmol/L) (Fig. 2), together with elevated serum parathyroid

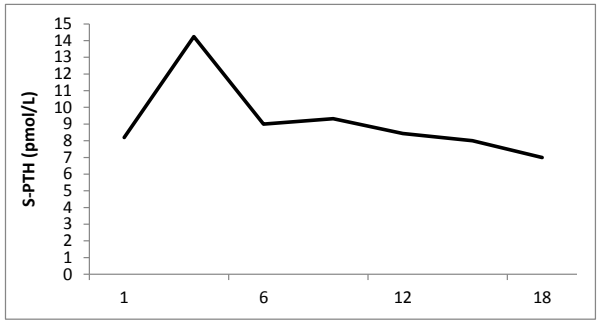


**Figure 3.** **Serum parathyroid hormone levels (S-PTH; pmol/L) assessed on a 3-monthly basis (reference values 1.6-7.2 pmol/L)**

hormone (S-PTH 8.2 pmol/L; normal 1.6–7.2 pmol/L) (Fig. 3). The boy was initially diagnosed as having epilepsy (complex partial seizures) and, due to CNS calcfications, Fahr´s disease. He was started on oral valproate therapy (300 mg/day) and calcium carbonate tablets (500 mg/day). Because of hypocalcaemia and hyperphosphataemia he was referred for further endocrinologic, metabolic and genetic examination. This confirmed hypocalcaemia with hyperphosphataemia and elevated S-PTH (Fig. 1-3), with normal S-ALP, S-creatinine and S-25(OH) vitamin D levels. Wrist X-ray was normal with appropriate bone age, no signs of demineralisation or osteomalacia, nor Albright´s hereditary osteodystrophy (AHO). His spinal bone mineral density (L1-L4 BMD) was normal (Dual X-ray absorptiometry – DXA Lunar - BMD L1-L4 0.991 g/cm$^2$ i.e. -0.1 SD Z-score). These findings clearly ruled out hypoparathyroidism, vitamin D-deficiency/osteomalacia, chronic kidney disease with metabolic bone disease (CKD-MBD), and clearly pointed to the diagnosis of pseudohypoparathyroidism (PHP). Patient therefore received additional oral calcium supplementation (total 2000 mg/day) and vitamin D therapy (oral cholecalciferol 20 000 IU/day). Three months later he experienced brief tetanic seizures lasting for two or three minutes and cramps, all triggered by physical activity. Computed tomography (CT) of the brain revealed massive calcifications of the basal ganglia, thalamus and nucleus dentatus, fully in accordance with MRI. There were delta waves episodes and sporadic theta waves on the EEG, interpreted as epileptic changes. Serum valproate level was low (174.7 mmol/L; therapeutic range 350-690 mmol/L), therefore valproate dosage was increased to 600 mg/day. As there was no improvement in S-Ca (Fig. 1), calcitriol (0.5 µg/day) was added to the treatment. Calcaemia was increasing slowly, together with gradual drop in S-P and S-PTH (Fig. 1-3). Significant improvement in speech, motoric coordination, muscle force and total absence of both twitching and Chvostek´s sign was apparent within the following six months. His school performance also improved. No further convulsions, neither cramps occurred and the valproate treatment was discontinued at the age of 14 years and 5 months.

Genetic examination ruled out Fahr´s disease as no mutations in the SLC20A2 gene were found. Mutational analysis of GNAS gene by Multiple-Ligation Probe amplification (MLPA) confirmed the diagnosis of pseudohypoparathyroidism type Ib (PHP Ib), due to methylation changes of exon I and GNAS promotor on 20q13.32. Therefore the appropriate diagnosis was pseudohypoparathyroidism type Ib with Fahr´s syndrome, but not Fahr´s disease.

Currently the boy is 18 years old, on daily calcium (1500 mg/day) and vitamin D supplementation (cholecalciferol 10 000 IU/day) and calcitriol (0.5 µg/day). His S-Ca, S-P and S-PTH are within reference ranges, he is free of convulsions, mentally fit (high school graduate), and physically very active, without any cramps or myalgias. There are no signs of nephrocalcinosis or urolithiasis on abdominal ultrasound.

## DISCUSSION

Hypocalcaemia due to vitamin D deficiency, hypoparathyroidism or PHP can lead to manifest tetany, presenting as epileptic seizures, together with muscle cramps and pain, severe muscle weakness, and psychomotor retardation.[1-9] Our patient was initially considered as suffering from epilepsy, however the abnormal values of calcaemia and phosphataemia pointed to another etiology of the convulsions and his neuromuscular and neuropsychic problems. The massive intracerebral calcifications were initially suggestive of Fahr´s disease, which is a rare heritable or sporadic neurodegenerative disorder characterized by basal ganglia calcification, and presenting with diverse neuropsychiatric manifestations. Calcifications may also occur in other brain regions, such as dentate nucleus, thalamus or cerebral cortex. Fahr's disease is caused by mutations in SLC20A2 gene, encoding sodium-dependent phosphate transporter 2 (PiT-2) that plays a major role in phosphate homeostasis by transporting phosphate across cell membranes.[10-12] Fahr's disease is usually inherited in an autosomal dominant pattern. Sporadic and autosomal recessive cases have been also reported. The diagnosis requires bilateral calcification of the basal ganglia associated with neuropsychiatric and motor symptoms and the absence of an underlying metabolic disorder. When the basal ganglia calcifications are secondary to a known cause, the disease is referred to as Fahr's syndrome.[10-12] In our patient Fahr´s disease was ruled out by the genetic examination. The laboratory results (low S-Ca, high S-P, high S-PTH) helped us to arrive at the diagnosis of PHP, which was later confirmed and detailed by MLPA as PHP Ib. The intracerebral calcifications were apparently due to PHP, therefore in this boy PHP and Fahr´s syndrome were the proper diagnoses.[13,14] Pseudohypoparathyroidism is defined as a receptor disorder with resistance to biological effects of PTH, leading to hypocalcaemia and hyperphosphataemia.[15,16] Pseudohypoparathyroidism is caused by the genetic defects of GNAS gene, encoding the alpha-subunit of the stimulatory G protein (Gsalpha), which is a signaling protein necessary for the biological actions of PTH. Pseudohypoparathyroidism is divided into two main types PHP-I and PHP-II. In PHP-I, the nephrogenous cyclic adenosine-monophosphate (cAMP) generation and phosphate urinary excretion after exogenous PTH administration are low in comparison to healthy population. There are two principal subtypes of PHP-I: these are PHP-Ia and PHP-Ib. Patients with PHP-Ia are characterised by Albright's hereditary osteodystrophy (AHO), consisting of obesity, short stature, soft tissue calcifications (brain, heart, kidney), brachydactyly and mental retardation. PHP Ia also includes hormonal abnormalities, such as hypothyroidism and hypogonadism caused by end organ resistance to thyroid-stimulating hormone (TSH) and gonadotropins. Pseudohypoparathyroidism Ib is caused by epigenetic changes at differentially methylated regions within GNAS, resulting in end organ resistance to biological effects of PTH, predominantly with no dysmorphic features. Scarcely, resistance to other hormones and variable features of AHO can also occur.[15-17] In PHP-II, cAMP generation in the kidney is normal, but the urinary excretion of phosphate is decreased. In all types of PHP, intracerebral calcifications usually occur.[13-15] The treatment is identical for patients with either PHP-Ia,b or PHP-II and rests in life-long calcium supplementation and administration of vitamin D.[15] In 2016 the EuroPHP network published a new classification to include all disorders with impairments in PTH and/or PTHrP signalling pathway, and these have been grouped under the term 'inactivating PTH/PTHrP signalling disorder' (iPPSD).[17]

Manifest tetany, masquerading as epilepsy, together with basal ganglia calcifications, occurs in patients with hypocalcaemic states, in particular in PHP. The serum evaluation of minerals, especially calcium and phosphate, should be performed in all patients with convulsions, cramps and psychomotor retardation. This is essential in arriving at a proper diagnosis and early initiation of appropriate treatment.

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