Exostosis and seizures in an adolescent refugee patient-case study of pseudohypoparathyroidism

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Summary Pseudohypoparathyroidism is a complex endocrine disorder caused by various possible biochemical receptor abnormalities of the parathyroid hormone. Phenotypical features that result depend heavily on the type of pseudohypoparathyroidism and genetic inheritance (maternal versus paternal inheritance). We discuss a case of an 18-year-old female refugee who presented as a new patient with multiple complaints including seizure disorder fitting the phenotypical syndrome known as Albright’s hereditary osteodystrophy. Allopathic treatment and theoretical osteopathic therapies that can be used are discussed.

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An 18-year-old Somalian female presented to the clinic for a new patient evaluation to establish care. She had recently arrived in the United States two weeks earlier. Her past medical history was significant for mental retardation, seizures since the age of 10 years, and notably short stature. She has been maintained with phenobarbital for seizures, with breakthrough seizure occurrences every two to three months.

Communication with the patient was facilitated with translator services. Her chief complaint was a rash that had been present for a few years, pain in her feet, and a painful lump on her side; she also needed refill prescriptions for her seizure medication. She also presented with records from the health department, which included a brief history from medical care she received at the refugee camp in Kenya where she lived before coming to the United States.

In reviewing the records, it was noted that she had no labs done in the past, aside from a phenobarbital level.

Family history was significant for blindness in the father, which was per records from infection; short stature in mother and brother; and no family history of seizure disorder.

Review of systems was also significant for loss of sight over time, slowly worsening without acute changes (per her mother).

Blood pressure was 92/56, pulse rate 88, respiratory rate 16, temperature 97.7, height was 54 inches and weight was 113 lbs.

Examination findings were: she was in mild distress over foot pain; her eyes were reactive to light, but with cataracts; her dentition had malocclusions and multiple caries; her heart and lungs were normal; the area of pain on the right side of her stomach was found to contain an osseous-like lump with thickened overlying skin; abdominal examination was otherwise normal; and skin examination was consistent with widespread dermatitis, showing a thin maculopapular rash. Here extremities were without edema, but here feet were noted to have shortened 3rd, 4th, and 5th metatarsals. Her hands had dimpling at the knuckles, with shortened 4th and 5th metacarpals. When her area of foot pain was examined under the fourth right metatarsal, it was found to be very tender, and palpable osseous deformity was noted to be consistent with bone spur, except with slightly mobility.

Radiographs of the affected foot (Fig. 1 and 2) were done in clinic and showed exostosis of the right 4th metatarsal, degenerative changes with bony erosion wide-
spread throughout the joints on the foot, and shortened metatarsals 3 to 5 on the right.

Labs including comprehensive metabolic panel, complete blood count, and phenobarbital level were ordered for history of seizure disorder. All labs were within normal ranges except the calcium level, which was 5.0 mg/dL. Because of the exostosis, low calcium, and shortened metatarsals, she was brought back for further work-up for parathyroid hormone (PTH), thyroid, magnesium, and phosphorus levels. As expected, PTH levels returned markedly elevated at 613 pG/mL (reference range 12-65) phosphorus elevated at 7.5 mg/dL (reference range 2.5-4.6) and thyroid-stimulating hormone returned elevated at 14.1 uIU/mL (reference range 0.5-4.5), with normal thyronine uptake, thyroxine, and free thyroxine index.

Based on history and physical and supporting laboratory studies, the patient was diagnosed with pseudohypoparathyroidism, specifically a subtype consistent with Albright’s hereditary osteodystrophy (AHO), with the phenotypical findings present at examination. The patient was referred to ophthalmology for her cataracts and to endocrinology for the pseudohypoparathyroidism. The rash was felt to be most likely caused by the phenobarbital as a result of the its continued use; a medication switch was attempted, but the patient missed the initial endocrine appointment and started having worsening seizures. Therefore, the rash was treated with steroid cream pending specialist input because neurologically she had been stable on phenobarbital for eight years, with rash occurring only after increased dosing two years previously, and the rash had not worsened. No biochemical tests were done to determine the specific type of pseudohypoparathyroidism.

**Discussion**

Pseudohypoparathyroidism is rare—no US prevalence data could be found—but a frequently cited estimated incidence based on one Japanese study is about 3.4 cases per one million people. Pseudohypoparathyroidism was first described by Fuller Albright and is characterized by resistance to parathyroid hormone, leading to elevated PTH levels, with clinically appearing hypoparathyroid as evidenced by hypocalcemia and hyperphosphatemia. Depending on the biochemical basis of the parathyroid resistance, different laboratory abnormalities and physical features may be present.

AHO refers to the phenotypical features associated with certain types of pseudohypoparathyroidism, specifically type 1a, type 1c, and pseudopseudohypoparathyroidism, which has normal PTH levels but shares the phenotype of AHO.

AHO has a profound clinical picture including brachydactyly sometimes of the 3rd but usually the 4th and 5th metacarpals and/or metatarsals; hypocalcemia, often with resultant seizure disorder that generally presents after age 5; short stature with rounded face; obesity; cataracts; dental hypoplasia; abnormal bone development; and subcutaneous ossification/exostosis.

The biochemical basis of all forms of pseudohypoparathyroidism relates to various mutations affecting the receptor for the parathyroid hormone, resulting in various levels of insensitivity to parathyroid hormone. There are five different forms of pseudohypoparathyroidism, only some of which have the AHO phenotype. Type 1a, which has the characteristic AHO phenotype, is related to many different potential missense mutations in the GNAS gene that encodes for the G subunit alpha (Gsα) responsible for generating cAMP as messenger for the PTH receptor. Because this is also needed in other hormone receptors such as thyroid-stimulating hormone receptors and growth hormone–releasing hormone receptors, patients with this subtype frequently show evidence of hypothyroidism and other hormone resistance disorders. Type 1c also has the characteristic phenotype, but has a different associated area of mutation described in the literature and demonstrates normal Gsα activity, whereas in type 1a, this activity is decreased to 50% of normal. There is some debate based on similarity of presentation and biochemical basis of whether type 1c is simply a subtype of 1a.9

Pseudopseudohypoparathyroidism has the phenotypical AHO phenotype, but without PTH resistance (although mildly elevated PTH levels can be present); therefore, hyperphosphatemia and seizures are not present and hypocalc-
cemia may or may not occur with age.\textsuperscript{10} The mutations that cause pseudopseudohypoparathyroidism are found on the same locus, but inheritance is paternal rather than maternal, leading to the hypothesis that imprinting plays a role in differing expression.\textsuperscript{5,6,8}

Pseudohypoparathyroidism type 1b shows PTH resistance without the phenotypical features of AHO, also has maternal inheritance, and can also show mild hypothyroidism.\textsuperscript{9,11} The area of mutation in 1b is believed to be outside the GNAS locus but still located on 20q.\textsuperscript{9} As with type 1b, type 2 does not display the phenotype of AHO but does show PTH resistance and can have a manifestation resembling rickets. Unlike type 1b, the defect is located distal to formation of cAMP, and cAMP excretion is elevated at baseline, with normal response in urinary cAMP to PTH.\textsuperscript{2}

Allopathic treatment is focused on symptomatic control and mainly consists of treatment for hypocalcemia, with calcium and cholecalciferol to help control tetany and seizures associated with PTH resistance.\textsuperscript{10} Indomethacin inhibits prostaglandin E\textsubscript{2} in inflammatory processes and may be helpful in decreasing incidence of exostosis.\textsuperscript{12} In addition, there is some indication that painful restricting exostoses can be removed surgically, although there is a risk of recurrence with this and trauma from removal may potentially worsen this aspect.\textsuperscript{12}

Osteopathic treatment for exostosis-related pain should focus on reestablishment of normal motion and function. Balanced ligamentous tension techniques to the metatarsals and the plantar fascia will alleviate dysfunction with minimal discomfort.\textsuperscript{3} Muscle energy techniques, if tolerated, will normalize motion at metatarsophalangeal joints. Evaluation of the pelvis and lower extremities will reveal compensatory changes and dysfunction, and these should be addressed. Relieving myofascial tension around the abdominal exostosis will relieve pain in this area as well.\textsuperscript{13}

**Conclusion**

Treating this patient illustrated the need to consider a complete medical history and constellation of symptoms, rather than focusing on the need to treat individual complications such as cataracts, bone pain, dental anomalies, and seizures. If the focus had been on complications rather than the overall clinical picture, a cause may not have been identified. This also demonstrates the need to consider disorders among our refugee populations, because typically this disorder would have been diagnosed at a much earlier age. In our case, although biochemical and genetic tests were not done to determine the subtype causing AHO, this most commonly fits type 1a pseudohypoparathyroidism, with the only other possibility, based on findings, being type 1c less likely given the concurrent hypothyroidism present.

**References**