Rathbun syndrome (hypophosphatasia) due to the heterozygous variant c.297+5G>A in alkaline phosphatase with unusual phenotype

Josef Finsterer¹, Claudia Stöllberger²

¹Department of Neurology, Klinik Landstrasse, Messerli Institute, Vienna, Austria; ²2nd Medical Department with Cardiology and Intensive Care Medicine, Klinik Landstrasse, Vienna, Austria.

To the Editor: Hypophosphatasia (HPP) is a musculoskeletal inborn error-of-metabolism caused by variants in alkaline phosphatase (ALPL) with reduced activity of the serum tissue-non-specific alkaline phosphatase,[¹] which is predominantly expressed in brain, muscle, bones, liver, and kidneys.[²] Accordingly, HPP is a multi-system disorder affecting bones and more rarely extra-osseus organs.[³] Osseous features of HPP include decreased bone quality, osteoid accumulations, reduced bone-mineralization, increased incidence of fractures, premature closure of sutures, bone deformities, dwarfism, Bechterew disease, early loss of teeth, intracranial hypertension, and prolonged bone healing.[¹] Extra-osseous features of HPP include seizures,[³] myopathy,[²] hepatopathy, and renal insufficiency. HPP responds favorably to enzyme replacement therapy with asotase-α.[¹]

The patient, who consented with the publication, is a polymorbid 49-year-old female, height 164 cm, weight 54 kg with a history of attention deficit hyperkinesia syndrome (ADHS) since early childhood, right ankle fracture in childhood, Hashimoto thyroiditis since age 26 years, bipolar disorder since age 29 years, slowly progressive muscle weakness with generalized myalgias and creatinekinase elevation up to 2500 U/L since age 30 years, low alkaline-phosphatase since at least age 34 years, hyperuricemia since age 36 years, arterial hypertension since age 39 years, breast cancer at age 40 years, hyperostosis frontalis recognized at age 40 years, ostealgia since age 43 years, moderate mitral insufficiency since age 47 years, and heart failure since age 49 years. The history was additionally positive for keratoconus, hyperlipidemia, and hiatal hernia. The family history was positive for breast cancer (mother, grandmother from mother side, great-grandmother from mother side), pancreas carcinoma (great aunt), diabetes (mother), myocardial infarction (mother), dementia (mother), osteopenia (mother), and polyarthritis (sister). None of the family members had features of HPP. At age 49 years she was admitted for exertional dyspnoea. X-ray of the lungs was normal. Electrocardiogram revealed QT-prolongation. Echocardiography revealed moderate mitral insufficiency and slightly reduced systolic function. Blood tests revealed hyper-Ckemia, hyperuricemia, hepatopathy, low alkaline phosphatase, and hyperlipidemia. Clinical neurologic exam revealed sore neck muscles and mild quadraparesis (M5-). Work-up for low alkaline phosphatase and ostegalia revealed the variant c.297+5G>A in ALPL. The patient was discharged with enalapril, hydrochlorothiazide, furosemide, atorvastatin, valproic acid, and midazolam. She had neither received asotase alfa nor did she undergo bone marrow transplantation.

The patient is interesting for adult-onset HPP with atypical features previously not described in association with HPP, such as ADHS, bipolar disorder, Hashimoto thyroiditis, arterial hypertension, hyperlipidemia, cancer, keratoconus, hyperlipidemia, hiatal hernia, heart failure, and QT-prolongation [Table 1]. Although it is conceivable that these features are attributable to the ALPL variant, they rather suggest that a second, so-far unidentified metabolic disease was present. Arguments for a second metabolic disease are that there were clinical manifestations in organs in which the expression of the enzyme is low (heart, eyes, endocrine organs, mamma), that these additional features have not been previously described in HPP, and that some family members manifested with these features but not with HPP. Hepatopathy was most likely due to the long-term treatment with valproic acid.

In conclusion, HPP may present with unusual features but the coincidence of two different disorders in the indexpatient cannot be excluded. Low serum alkaline-phosphatase together with ostegalia should prompt clinicians to consider HPP.

Correspondence to: Josef Finsterer, Klinik Landstrasse, Messerli Institute, Postfach 20, 1180 Vienna, Austria
E-Mail: fifiga1@yahoo.de

© 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2022;135(3)
Table 1: Phenotypic features of HPP previously reported and in the index patient.

| Feature                    | Children | Adults | Reference                          | Index patient |
|----------------------------|----------|--------|------------------------------------|---------------|
| Myopathy                   | Yes      | Yes    | Fonta et al.[2]                    | Yes           |
| Hyperuricemia              | No       | Yes    | Krohn-Grimberghe et al.[4]         | No            |
| Premature closure of sutures | Yes    | Yes    | Krohn-Grimberghe et al.[4]         | No            |
| Bone deformities           | Yes      | Yes    | Krohn-Grimberghe et al.[4]         | No            |
| Dwarfism                   | Yes      | Yes    | Krohn-Grimberghe et al.[4]         | No            |
| Bechterew syndrome         | No       | Yes    | Krohn-Grimberghe et al.[4]         | No            |
| Early loss of teeth        | Yes      | Yes    | Krohn-Grimberghe et al.[4]         | No            |
| Spinal hyperostosis        | No       | Yes    | Krohn-Grimberghe et al.[4]         | No            |
| Chondrocalcinosis          | Yes      | Yes    | Krohn-Grimberghe et al.[4]         | No            |
| Intracranial hypertension  | Yes      | Yes    | Collmann et al.[5]                | No            |
| Prolonged bone healing     | No       | Yes    | Stürznickel et al.[1]             | No            |
| Seizures                   | Yes      | Yes    | Fonta et al.[2]                    | No            |
| Renal failure              | No       | Yes    | Whyte et al.[6]                    | No            |
| ADHS                       | No       | No     | –                                  | Yes           |
| Bipolar disorder           | No       | No     | –                                  | Yes           |
| Hashimoto                  | No       | No     | –                                  | Yes           |
| Keratokonus                | No       | No     | –                                  | Yes           |
| Hyperostosis frontalis     | No       | No     | –                                  | Yes           |
| Arterial hypertension      | No       | No     | –                                  | Yes           |
| Hyperlipidemia             | No       | No     | –                                  | Yes           |
| Breast cancer              | No       | No     | –                                  | Yes           |
| Heart failure              | No       | No     | –                                  | Yes           |
| Mitral insufficiency       | No       | No     | –                                  | Yes           |
| QT-prolongation            | No       | No     | Index case                         | Yes           |

ADHS: Attention deficit hyperkinesia syndrome; HPP: Hypophosphatasia; Ped: Pediatric cases; –: Not available.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s)/patient’s guardians has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the article. The patients/patient’s guardians understand that their names and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

Conflicts of interest

None.

References

1. Stürznickel J, Schmidt FN, von Vopelius E, Delsmann MM, Schmidt C, Jandl NM, et al. Bone healing and reactivation of remodeling under astatase alfa therapy in adult patients with pediatric-onset hypophosphatasia. Bone 2021;143:115794. doi: 10.1016/j.bone.2020.115794.

2. Fonta C, Salles JP. Neuromuscular features of hypophosphatasia. Arch Pediatr 2017;24:3585–3588. doi: 10.1016/S0929-693X(18)30021-6.

3. Sharma N, Bache E, Clare T. Bilateral femoral neck fractures in a young patient suffering from hypophosphatasia, due to a first time epileptic seizure. J Orthop Case Rep 2015;5:66–68. doi: 10.13107/jocr.2250-0685.312.

4. Krohn-Grimberghe B, Ludwig B, Furkert D. Rathbun-Syndrom (Hypophosphatasie). Klinisch: Minderwuchs und Bechterew-Symptoma HPP; Hypophosphatasia. Z Rheumatol 1991;50:387–391.

5. Collmann H, Mornet E, Gattenlöhner S, Beck C, Girschick H. Neurosurgical aspects of childhood hypophosphatasia. Childs Nerv Syst 2009;25:217–223. doi: 10.1007/s00381-008-0708-3.

6. Whyte MP, Leelawattana R, Reinus WR, Yang C, Mumm S, Novack DV. Acute severe hypercalcemia after traumatic fractures and immobilization in hypophosphatasia complicated by chronic renal failure. J Clin Endocrinol Metab 2013;98:4606–4612. doi: 10.1210/jc.2013-1811.

How to cite this article: Finsterer J, Stöllberger C. Rathbun syndrome (hypophosphatasia) due to the heterozygous variant c.297+5G>A in alkaline phosphatase with unusual phenotype. Chin Med J 2022;135:377–378. doi: 10.1097/CM9.000000000001777