

Hyperhomocysteinemia secondary to cystathionine beta-synthetase deficiency. Presentation of an atypical case

Hiperhomocisteinemia secundaria a deficiencia de cistationina β-sintetasa. Presentación de un caso atípico

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Summary
We describe the case of a 2-year-old boy with neurodevelopmental delay, in whom brain MRI showed diffuse white matter changes, diffusion restriction, and hyperintensity of the medial tegmental tract, prior to the diagnosis of hyperhomocysteinemia secondary to Cystathionine beta-synthase deficiency (classic homocystinuria). These findings are not typically described in this disorder, so its diagnosis may be delayed. This case illustrates the need to consider classical homocystinuria in the differential diagnosis of childhood white matter diseases, as well as within the causes of central tegmental tract hyperintensity.

Resumen
Se describe el caso de un niño de 2 años de edad con retraso en el neurodesarrollo, en quien mediante resonancia magnética (RM) cerebral se observaron cambios difusos de la sustancia blanca, restricción a la difusión y alta señal del tracto tegmentario central, antes del diagnóstico de hiperhomocisteinemia secundaria a deficiencia de cistationina β-sintetasa (homocistinuria clásica). Dichos hallazgos no son típicos de este trastorno, por lo que su diagnóstico puede retrasarse. Este caso ilustra la necesidad de considerar la homocistinuria clásica en el diagnóstico diferencial de las enfermedades de la sustancia blanca infantil, así como entre las causas de alta señal del tracto tegmentario central.

Case Report

Male patient, 2 years old. Product of the second pregnancy, which was high risk due to gestational diabetes and decreased growth velocity in the last trimester. Maternal serologies were negative. Pregnancy supplemented with multivitamins and no exposure to teratogens. The baby was born at 34 weeks by cesarean section due to circular neck and premature rupture of membranes, weighing 2700 g and measuring 47 cms. Neonatal thyroid stimulating hormone (TSH) was normal. She did not undergo extended neonatal screening. As family history, her parents were non-consanguineous, the older brother was healthy at 8 years of age and she had paternal second-line cousins with Parkinson's disease. From the age of 2 years the mother noticed developmental delay, especially in the area of language. In the evaluation by Neurology, a simple brain magnetic resonance imaging (MRI) with spectroscopy was performed, which showed an increase in the occipitofrontal diameter, with a dimension of 163 mm (Figure 1); although it did not meet the criteria for macrocephaly, it was at the upper limit of normality (normal range for age Percentile 3 of 132.3 mm to Percentile 97 of 168.5 mm) (1). Additionally, the T1 sequence showed delayed myelination expected for the age of the patient (Figure 2), which corresponded to an approximate age of 12 months. In the T2 sequence (Figure 3) diffuse alteration in the signal intensity of the white matter was identified, with special involvement of the U-fibers and the corpus callosum; however, the deep white matter was found to be normal.

High signal of the central tegmental tracts was observed. Diffusion (Figure 4) showed restriction in the same white matter areas that had high signal in T2, with involvement of the corpus callosum and central tegmental tracts. Spectroscopy was normal for age (Figure 5), there was no alteration of metabolites, the N-acetyl-aspartate-choline (NAA-Co) ratio was normal and no lactate peak was observed. With these findings, a neurometabolic disease was considered, given the increased head circumference, altered white matter signal intensity and areas of diffusion restriction. Among the possibilities, Canavan disease was considered, but spectroscopy did not find significant elevation of N-acetyl-aspartate (NAA) to confirm this diagnosis. On the other hand, high signal

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had been evidenced in the central tegmental tract, a finding that has been described in pathologies such as non-ketotic hyperglycinemia, mitochondrial disorders, methionine adenosyltransferase deficiency, evanescent white matter disease; it has also been postulated that it could represent a physiological variant of brain development (2, 3).

Metabolic and genetic studies were performed. The karyotype was 46 XY, normal very long chain fatty acids, normal arylsulfatase. Methionine 971 µmol/L, homocysteine 170 µmol/L, the latter were found to be elevated, so complete sequencing of the CBS (cystathionine β-synthetase) gene was performed, which showed the mutations c. 572C>T/ c. 362G>A, both pathogenic, leading to the diagnosis of hyperhomocysteinemia caused by cystathionine β-synthetase deficiency. Ophthalmologic examination was normal. Since then she has been on dietary treatment with supplements, pyridoxine 50 mg/day, folic acid 5 mg/day, betaine 2 grams + HCISMED -B and cyanocobalamide IM monthly. She is currently stable, with neurodevelopmental improvement.



Figure 1. Sagittal midline sagittal T1-weighted sequence: increased occipitofrontal diameter at the upper limit of normal (normal range for age P 3 of 132.3 mm-P 97 of 168.5 mm).

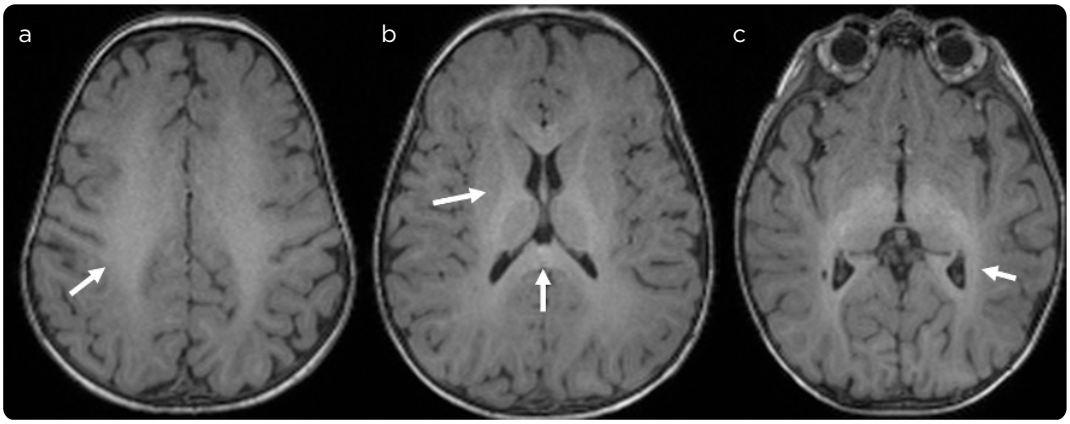


Figure 2. T1-weighted sequence, axial slices. a, b and c) Delayed myelination expected for the patient's age. This myelination pattern corresponds to an approximate age of 12 months.

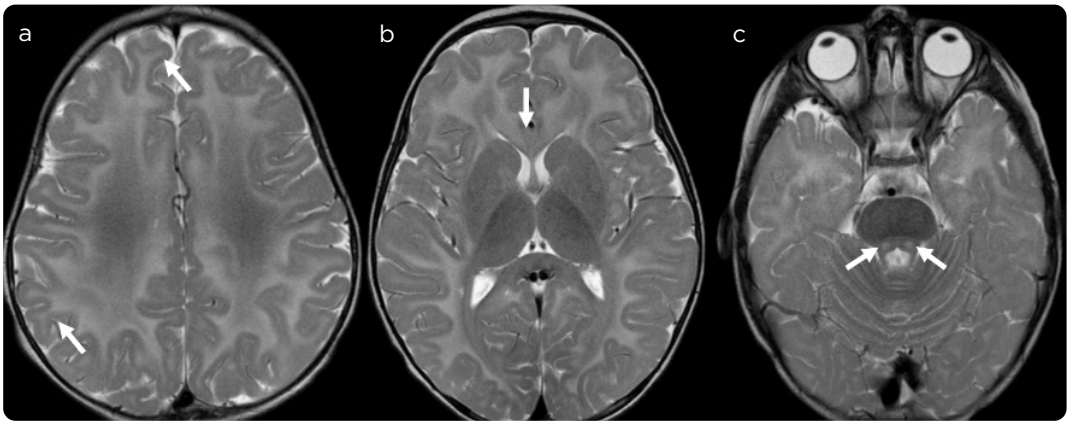


Figure 3. T2-weighted sequence, axial slices. a and b) Alteration in the signal intensity of the white matter in diffuse form, high signal, with involvement of U-shaped fibers and the corpus callosum (arrows). The deep white matter has normal signal. c) High signal of the central tegmental tracts (arrow).

[1]Methionine-free powdered infant formula supplemented with cystine for the nutritional treatment of children over one year of age with homocystinuria. Contains homocystinuria.

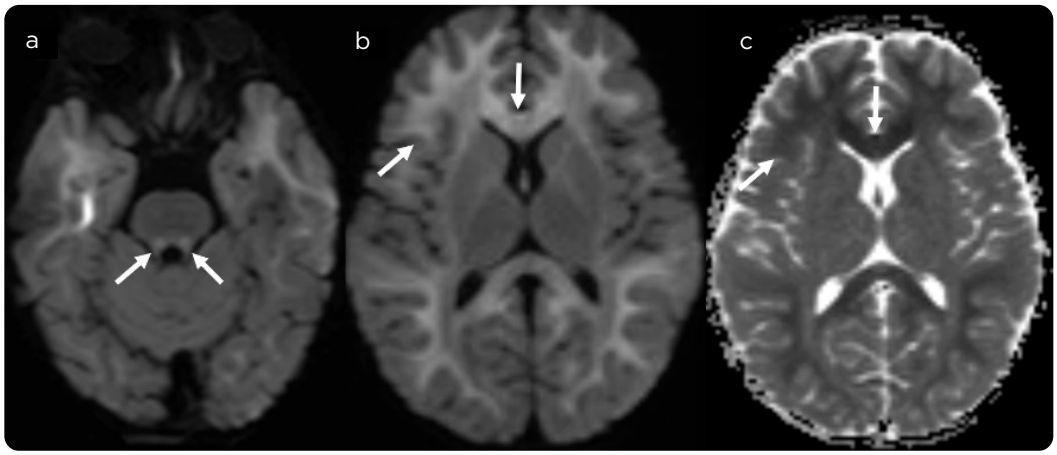


Figure 4. Diffusion sequence and ADC map, axial sections. a) Diffusion restriction in central tegmental tracts (arrow). b and c) Diffusion restriction of the white matter with high signal in T2 (images presented in figure 3). There is involvement of U-shaped fibers and the corpus callosum. The deep white matter is respected.

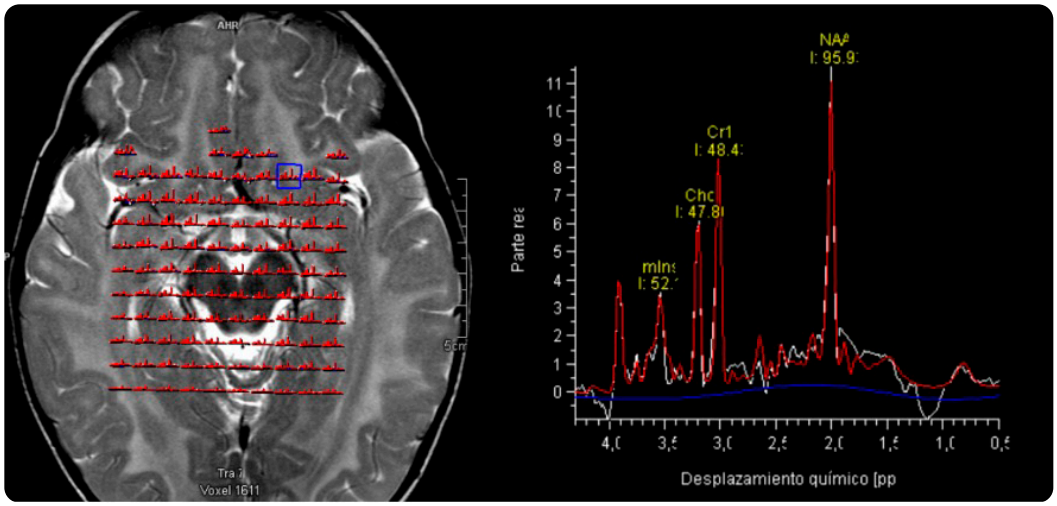


Figure 5. Multivoxel spectroscopy. Intermediate echo time (135 ms). Multiple samples were taken in the compromised white matter, without evidence of alteration of metabolites. The NAA-Co ratio is normal. No lactate peak is observed.

Discussion

Definition and physiopathology

Hyperhomocysteinemia, formerly known as homocystinuria, comprises a group of inherited disorders of homocysteine metabolism, a non-structural amino acid that is formed in the methionine catabolic pathway and is key in the methionine trans-sulfuration and remethylation pathways. Homocysteine can be recycled into methionine (remethylation pathway) or catabolized into cystathionine, cysteine and sulfate (trans-sulfuration pathway) (3). The three enzymes involved in the pathogenesis of hyperhomocysteinemia are cystathionine β-synthetase in the trans-sulfuration pathway, methionine synthetase and 5,10-methylene tetrahydrofolate reductase in the remethylation pathway; folate, vitamins B12 (cobalamin) and B6 (pyridoxine) play a role as cofactors (4, 5).

In the case described here, hyperhomocysteinemia was confirmed to be secondary to cystathionine β-synthase deficiency, also known as classical homocystinuria. It is a rare, autosomal recessive disease. Its epidemiology is widely varied, depending on ethnicity and method of diagnosis. The estimated population frequency is approximately 1:1800 to 1:900,000 depending on the incidence of births of patients detected by neonatal screening and/or later diagnosis (6).

The pathophysiology is not well understood, but it has been thought that homocysteine accumulation leads to an increase in s-adenosylhomocysteine (the step prior to conversion to homocysteine), thus favoring re-methylation to methionine and depletion of cystathionine and cysteine, which is associated with increased apoptosis, oxidative stress and alterations of structural proteins such as fibrillin, which may contribute to connective tissue abnormalities. Additionally, it has been shown that elevated homocysteine levels modify the sulphohydryl groups in proteins and interfere with the cross-linking of sulphohydryl groups in proteins such as elastin, which could explain the dislocation of the crystalline lens and skeletal abnormalities that characterize the disease (7).

Clinical Presentation

The clinical picture depends on the level of enzyme activity, has a multisystemic presentation and has been classified according to the patient's response to the pyridoxine challenge test.

Ocular involvement is characteristic, in which the initial manifestation may be progressive myopia, commonly severe, with onset in the first year of life. Ectopia lentis can also be found later, around 8 years of age; this catastrophic evolution is usually related to patients who do not respond to vitamin B6 (8, 9).

From the skeletal point of view, a marfanoid habitus, osteoporosis and bone deformities such as pectus excavatum or carinatum, genu valgum and scoliosis are identified (10). In the central nervous system, psychomotor retardation and/or intellectual disability, seizures, extrapyramidal signs and psychiatric and behavioral problems are identified, of which anxiety disorder, obsessive compulsive disorder, depression and psychotic episodes are difficult to manage in patients who do not respond to vitamin B6 therapy (11). On the other hand, the vascular system is also frequently involved, thromboembolism is the representative outcome, with a major cause of morbidity and mortality in patients. Venous thrombosis is more frequent than arterial thrombosis and can occur in any part of the body; additionally, half of the patients treated will suffer a stroke before the age of 30 years (4, 12, 13). In the case described, the presentation consisted only of neurodevelopmental delay, which made it difficult to suspect the disease clinically.

Findings in images

Multiple lacunar and larger infarcts are commonly reported, usually at different stages and involving different vascular territories, with a predilection for the periventricular region; such findings are not specific, but the age of presentation is unusual, which makes the diagnosis suspicious. A higher incidence of spontaneous arterial dissection has also been reported (14-16). On the other hand, demyelination, vacuolization and spongy degeneration of the white matter have been described. This finding is usually associated more with hyperhomocysteinemias secondary to 5,10-methylenetetrahydrofolate reductase deficiency and disorders of intracellular cobalamin metabolism.

Little has been reported about its presentation in cystathionine β-synthetase deficiency (17, 18). Diffuse white matter edema is evident on imaging, with high signal on T2-weighted sequences, with or without diffusion restriction. These abnormalities are bilateral, but not necessarily symmetrical; they most frequently involve the periventricular white matter, but in some cases they extend to the U-fibers (16).

In this case, the most representative imaging findings consisted of diffuse alteration of the signal intensity of the white matter with involvement of U-shaped fibers and corpus callosum and with restriction to diffusion in the involved areas, rare findings, which have been found more in other types of hyperhomocysteinemia, and which have been rarely described in cystathionine β-synthetase deficiency (17, 18). Therefore, although in this case it is not a typical presentation, since no vascular, ocular or skeletal disorders are found, these changes in the white matter should be taken into account within the imaging spectrum of cystathionine β-synthetase deficiency and, likewise, include this disease in the differential diagnosis of diffuse white matter involvement of metabolic origin, which is broad and challenging.

Additionally, the high signal in T2-weighted sequences of the central tegmental tract was found, a non-specific sign that has even been postulated as a physiological variant of brain development (3), but that has also been documented in multiple pathologies, such as methionine adenosyltransferase I/III deficiency, nonketotic hyperglycinemia, maple syrup urine disease, tetrahydrobiopterin deficiency, mitochondrial encephalopathy, evanescent white matter disease, epilepsy, vigabatrin use, and hypoxic ischemic encephalopathy (2, 3); however, it has not been described in cystathionine β-synthetase deficiency, so it is considered that more studies should be performed to verify its presence in this disorder and, thus, include the pathology in the differential diagnosis of such a finding.

For all of the above, it is important to emphasize that the diagnosis of the case presented should be based on clinical suspicion, biochemical and imaging findings, and finally confirmation by molecular genetic testing.

Relevant biochemical tests and molecular genetics

Within the biochemical arsenal, in the first instance is the measurement of plasma total homocysteine levels, considering that free homocysteine levels should not be requested, since its elevation will occur if and only if total homocysteine values are above 50-60 μmol/L. Plasma levels of methionine are also evaluated, which will be elevated or at the upper limit; as well as low plasma cystathionine concentrations and an elevated methionine/cystathionine ratio will be evident. In the patient in this case, both plasma total homocysteine and methionine were elevated (19).

The definitive diagnosis is confirmed by molecular genetic testing that identifies pathogenic variants in the CBS gene encoding the deficient enzyme, either by sequencing analysis or duplication/deletion variant studies targeting the affected gene. In cases of high clinical suspicion, but with inconclusive molecular study, the measurement of enzyme activity in fibroblasts can be used (20).

Treatment

After identification of the enzyme defect, referral should be made to a multidisciplinary center with expertise in inborn errors of metabolism with a genetics service. It should be evaluated whether or not there is a response to the use of pyridoxine (vitamin B6) as a therapeutic test. In addition, it is important to identify whether there is associated folate and vitamin B12 deficiency and correct it, since under normal conditions it optimizes the conversion of homocysteine to methionine by methionine synthase, thus decreasing the concentration of homocysteine in plasma. Betaine treatment provides an alternative remethylation pathway to convert excess homocysteine to methionine and may help prevent complications, particularly thrombosis. Its use may be considered in patients who have failed to comply with the methionine exclusion diet and/or are non-responders to pyridoxine (21).

Conclusion

A case of hyperhomocysteinemia secondary to cystathionine β-synthetase deficiency (classic homocystinuria) was described with unusual findings in brain MR imaging, consisting of diffuse alteration of the signal intensity of the white matter with involvement of U-shaped fibers and corpus callosum, with respect to the periventricular white matter and diffusion restriction in the involved areas, in addition to high signal in the central tegmental tract. It is considered that, although these features are uncommon in cases of classic homocystinuria, they

should be taken into account in the diagnostic approach and, in some cases supported by clinical findings, they should be included in the imaging spectrum of this pathology.

References

1. Garel C, Cont I, Alberti C, Josserand E, Moutard ML, Ducou le Pointe H. Biometry of the corpus callosum in children: MR imaging reference data. AJNR Am J Neuroradiol. 2011;32(8):1436-43. doi: https://doi.org/10.3174/ajnr.A2542
2. Yoshida S, Hayakawa K, Yamamoto A, Aida N, Okano S, Matsushita H, et al. Symmetrical central tegmentario tract (CTT) hyperintense lesions on magnetic resonance imaging in children. Eur Radiol. 200919(2):462-9. doi: https://doi.org/10.1007/s00330-008-1167-7
3. Aguilera-Albesa S, Poretti A, Honnef D, Aktas M, Yoldi-Petri ME, Huisman TA, et al. T2 hyperintense signal of the central tegmentario tracts in children: disease or normal maturational process? Neuroradiology. 2012;54(8):863-71. doi: https://doi.org/10.1007/s00234-012-1006-z
4. Barkovich AJ Raybaud C. Pediatric neuroimaging. Sixth ed. Philadelphia: Wolters Kluwer; 2019.
5. Bublil EM, Majtan T. Classical homocystinuria: From cystathionine beta-synthase deficiency to novel enzyme therapies. Biochimie. 2020;173:48-56. doi: https://doi.org/10.1016/j.biochi.2019.12.007
6. Weber Hoss GR, Sperb-Ludwig F, Schwartz IVD, Blom HJ. Classical homocystinuria: A common inborn error of metabolism? An epidemiological study based on genetic databases. Mol Genet Genomic Med. 2020;8(6):e1214. doi: https://doi.org/10.1002/mgg3.1214
7. Sacharow SJ, Picker JD, Levy HL. homocystinuria caused by cystathionine beta-synthase deficiency. En: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviewsÆ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.
8. Morris AA, Kožich V, Santra S, Andria G, Ben-Omran TI, Chakrapani AB, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis. 2017;40(1):49-74. doi: https://doi.org/10.1007/s10545-016-9979-0
9. Rahman M, Sharma M, Aggarwal P, Singla S, Jain N. Homocystinuria and ocular complications - A review. Indian J Ophthalmol. 2022;70(7):2272-8. doi: https://doi.org/10.4103/ijo.IJO_309_22
10. Lindstrom K, Ficicioglu C, Kaplan P, Freehauf CL, Levine MA. Low bone mineral density is a common finding in patients with homocystinuria. Mol Genet Metab. 2016;117:351-4.
11. Diaz-Arrastia R. Homocysteine and Neurologic Disease. Arch Neurol. 2000;57(10):1422-7. doi: https://doi.org/10.1001/archneur.57.10.1422
12. Stephan JL. Inaugural cerebral sinovenous thrombosis revealing homocystinuria in a 2-year-old boy. J Child Neurol. 2015;30:107-12.
13. Karaca M, Hismi B, Ozqul RK, Karaca S, Yilmaz DY, Coskun T, et al. High prevalence of cerebral venous sinus thombosis (CVST) as presentation of cystathionine beta-synthase deficiency in childhood: molecular and clinical findings of Turkish probands. Gene. 2014;534:197-203.
14. Reddy N, Calloni SF, Vernon HJ, Boltshauser E, Huisman TAGM, Soares BP. Neuroimaging findings of organic acidemias and aminoacidopathies. Radiographics. 2018;38(3):912-31. doi: https://doi.org/10.1148/rg.2018170042
15. Li CQ, Barshop BA, Feigenbaum A, Khanna PC. Brain magnetic resonance imaging findings in poorly controlled homocystinuria. J Radiol Case Rep. 2018;12(1):1-8. doi: https://doi.org/10.3941/jrcr.v12i1.3207
16. Knaap MS van der., Valk J, Barkhof F. Magnetic resonance of myelination and myelin disorders. 3rd ed. Springer; 2005.
17. Brenton JN, Matsumoto JA, Rust RS, Wilson WG. White matter changes in an untreated, newly diagnosed case of classical homocystinuria. J Child Neurol. 2014;29(1):88-92. doi: https://doi.org/10.1177/0883073812465012
18. Ismayilova N, MacKinnon AD, Mundy H, Fallon P. Reversible cerebral white matter abnormalities in homocystinuria. JIMD Rep. 2019;44:115-9. doi: https://doi.org/10.1007/8904_2018_135
19. Watkins D, Rosenblatt DS. Inherited disorders of folate and cobalamin transport and metabolism. En: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson K, Mitchell G, eds. The online metabolic and molecular bases of inherited disease (OMMBID). New York, NY: McGraw-Hill; 2014. Cap. 155.
20. Gerrard A, Dawson C. Homocystinuria diagnosis and management: it is not all classical. J Clin Pathol. 2022. doi: https://doi.org/10.1136/jcp-2021-208029
21. Majtan T, Kožich V, Kruger WD. Recent therapeutic approaches to cystathionine beta-synthase-deficient homocystinuria. Br J Pharmacol. 2022. doi: https://doi.org/10.1111/bph.15991

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