Hypocalcaemia Induced Optic Neuropathy in a Patient with Undiagnosed HDR Syndrome

Emmanuel Ssemmondo[1], Jonathan Thow[1], Anis Abobaker[2]* and Greg Heath[3]

[1]Endocrinology Department, York and Scarborough Teaching Hospitals NHS Foundation Trust, York, the UK

[2]Internal medicine, Piedmont Athens Regional Medical Centre, Athens, the USA

[3]Ophthalmology Department, York and Scarborough Teaching Hospitals NHS Foundation Trust, York, the UK

Received: 27 February 2023

Accepted: 11 May 2023

*Corresponding author: anis.abobaker@yahoo.com

DOI 10.5001/omj.2024.33

Abstract

Hypocalcaemia, Deafness and Renal (HDR) syndrome - also known as Barakat syndrome - is an autosomal dominant genetic condition characterised by hypocalcaemia, sensorineural hearing loss and renal dysplasia. Papilledema (optic disc swelling secondary to raised intracranial pressure) secondary to hypocalcaemia-induced intracranial hypertension has been reported in literature. Optic disc oedema secondary to hypocalcaemia-induced optic neuropathy with normal intracranial pressure is rare. Herein we present a rare case of HDR syndrome. To the best of our knowledge, this may be the first case of HDR syndrome diagnosed following presentation with hypocalcaemia- induced optic disc oedema. We propose that serum calcium levels should be analysed in patients suspected of harbouring optic disc oedema who are referred for further neurological investigations as early diagnosis and correction of hypocalcaemia may improve the signs and symptoms of their optic nerve disease.

Keywords: Optic Neuropathy; Hypoparathyroidism; Hypocalcaemia; GATA3 Gene.

Introduction

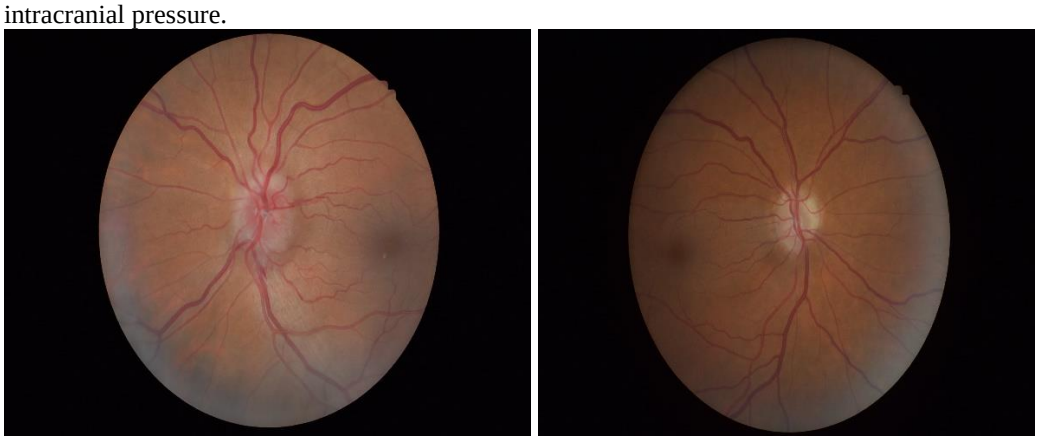
Hypoparathyroidism, Sensorineural deafness and Renal dysplasia (HDR) syndrome (also known as Barakat Syndrome) is a rare autosomal dominant genetic condition with patients manifesting with different degrees of renal impairment, sensorineural deafness and hypocalcaemia. Cases of optic disc oedema associated with hypoparathyroidism have previously been documented in the literature (1, 2). In some cases, intracranial hypertension secondary to hypocalcaemia has been implicated leading to true papilloedema (2). Ascertaining a diagnosis of hypocalcaemia- induced optic neuropathy may be delayed in such cases since patients do not present with typical neurological symptoms related to hypoparathyroidism (2). In this report, we present a rare case of HDR syndrome, highlighting how clues in the patient's background history guided appropriate genetic testing and diagnosis.

Case Report

A 52-year-old Caucasian man was referred by his optometrist to the local hospital's ophthalmology department. He presented with an 8-month history of blurring of vision in the left eye. The symptoms had more recently been associated with discomfort behind the left eye, which was worse with eye movements. He reported tunnelling down to greyness of the left vision for about 5 seconds when he stood up but improving thereafter. He also complained of a headache which was worse on bending forward or coughing and better at rest/lying down. His past medical history included a previous, presumptive, diagnosis of idiopathic intracranial hypertension and he had received acetazolamide intermittently for this. He was known to suffer loss of his right inferior visual field which was assigned to the aforementioned, presumed neurological diagnosis. He was also previously diagnosed with schizoaffective disorder and drug (marijuana) - induced psychosis, which was treated with risperidone. He

was also hypertensive. Current medication included over the counter calcium supplements. He consumed minimal alcohol and he was a smoker. There was no family history of ocular or systemic disease.

He appeared relatively well in the ophthalmology clinic. His blood pressure was 173/107 mmHg and he was apyrexial. His visual acuities were 6/5 and 6/9 in the right and left eyes respectively. He manifested a right relative afferent pupillary defect. There was no evidence of dyschromatopsia and his intraocular pressures were normal at 17mmHg in both eyes. Visual field analysis revealed a stable, absolute inferior altitudinal defect and a relative enlargement of the blind spot in his right and left eyes respectively. His left optic nerve head appeared swollen and his right nerve head displayed generalised pallor but no swelling (figure 1). There were no other abnormal neurological signs noted on examination. He was reported to have sensorineural hearing loss although the details were not available at the time of presentation. Examination of his chest, cardiovascular system as well as the abdomen were unremarkable. The patient was referred to the medical team to be investigated for possible raised intracranial pressure.



Left optic disc at presentation Right optic disc at presentation

Figure 1: showing appearances of discs at presentation.

Further investigations revealed; full blood count was normal, C reactive protein (CRP) was 9mg/l with a normal plasma viscosity. Urea, Thyroid function, Haemoglobin A1C and ferritin were all normal (see Table 1). The bone profile showed an adjusted calcium of 1.74mmol/l (normal range 2.20-2.60). His phosphate was 1.76mmol/l (normal is 0.80-1.50mmol/l) with a normal alkaline phosphatase of 100IU/l (normal 30-130). Parathyroid hormone was inappropriately normal at 3.0pmol/l (1.6-6.9), with a low Vitamin D level of 19nmol/l (normal >51). The patient underwent a CT of his head which failed to elicit any features compatible with raised intracranial pressure. A lumbar puncture revealed an opening pressure of 22cm and closing pressure of 18cm of cerebral spinal fluid with normal constituents.

Table 1: Blood results on initial presentation.

Item (units)	**Result**	**Reference range**
ALP (IU/L)	100	30-130
ALT (U/L)	12	0-45
Bilirubin (umol/l)	4	<21
K+ (mmol/l)	4.5	3.5-5.3
Creatinine (umol/l)	110	59-104
Urea (mmol/l	5.5	2.5-7.8
CRP (mg/l)	9	0-5
Plasma viscosity (mPa.s)	1.58	1.50-1.72
Phosphate (mmol/l)	1.76	0.80-1.50
Vitamin D (nmol/l)	19	>51
HbA1C (mmol/mol)	38	20-41
TSH (mU/l)	0.8	0.27-4.20
Free T4 (pmol/l)	22	11-22
Ferritin (microgram/l)	51	30-400

The patient was discussed with the endocrine team and a diagnosis of hypocalcaemia secondary to hypoparathyroidism was made. Advice was given over the phone and an outpatient appointment arranged. Subsequent review by the Ophthalmology team made a diagnosis of left optic nerve head swelling and previous right optic atrophy due to hypocalcaemic optic neuropathy. The latter finding was attributed to previous ischaemia induced by previous optic disc oedema. The patient was treated as an outpatient with alfacalcidol (1 microgram once a day) and oral calcium supplements.

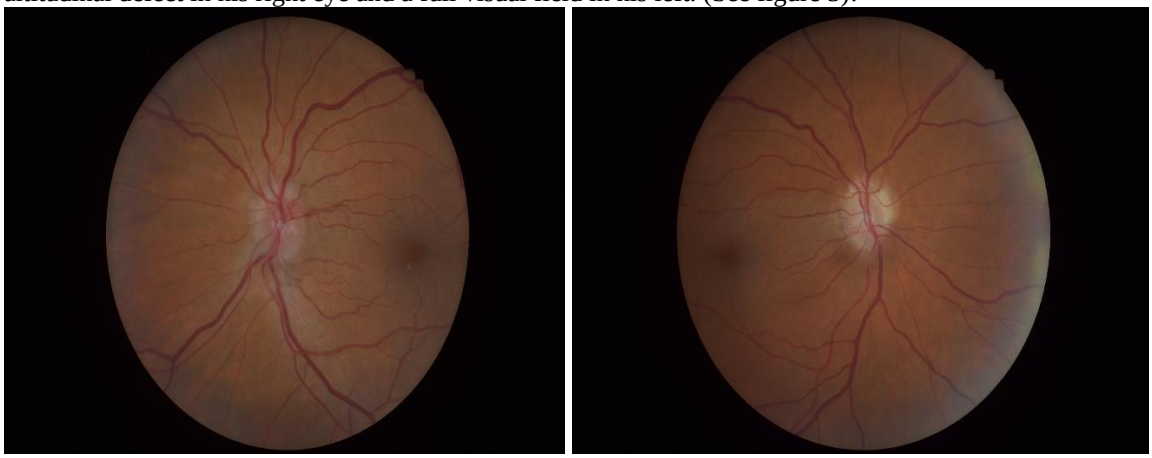
The patient was reviewed in the Endocrine clinic. A detailed past medical and family history was taken. This revealed that he had sensorineural deafness. His son received treatment for hypoparathyroidism and deafness while his daughter was diagnosed with end stage kidney disease secondary to renal dysplasia in addition to hypocalcaemia (although she was never formally referred to endocrinology). Furthermore, she underwent bilateral cataract extraction when she was 10 years old. There was no family history of cataracts and the most likely cause for her ocular presentation was persistent hypocalcaemia.

A renal ultrasound revealed a hypoplastic left kidney but analysis of his renal function was unremarkable. Genetic testing revealed that the patient was heterozygous for a pathogenic GATA3 variant, confirming a diagnosis of autosomal dominant HDR syndrome. His family members were contacted and referred to a clinical genetics service. His calcium levels were measured during follow up and this continued to improve (see Table 2). He also reported substantial improvement in cognition and overall well-being.

Table 2: Adjusted calcium levels during follow up.

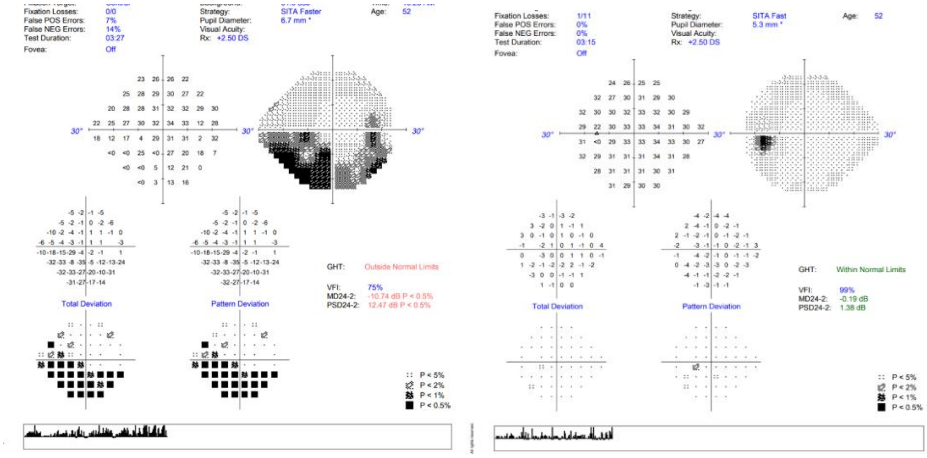
Date	**Adjusted Calcium (mmol/l) Ref(2.20-2.60)**
23.12.2021	1.74
24.12.2021	2.09
06.01.2022	1.91
17.01.2022	1.91
24.01.2022	2.02
15.02.2022	2.17
24.03.2022	2.41

He was reviewed in the eye clinic 3 weeks following the initial assessment. His visual acuities were 6/6 and 6/9 in his right and left eyes respectively. His left optic nerve head appearance demonstrated a reduction in his optic nerve head swelling. Appearances of the optic discs following treatment are shown in figure 2 below. At the latest review, his calcium was 2.41. His left optic nerve head swelling had also resolved. The right optic disc demonstrated generalised mild optic disc pallor (from previous ischaemic optic neuropathy) but no swelling. His final visual acuities were 6/4 and 6/7.5 in the right and left eyes respectively (which have improved compared to the initial presentation to the ophthalmology clinic). Visual field assessment uncovered a stable, inferior, absolute altitudinal defect in his right eye and a full visual field in his left. (See figure 3).



Left optic disc post treatment Right optic disc post treatment

Figure 2: Optic discs following hypocalcaemia treatment.



Right Visual field Left Visual Field

Figure 3: Visual fields post treatment which showed a stable, inferior, absolute altitudinal defect in his right eye and a full visual field in his left.

Discussion

Our patient harboured hypoparathyroidism and deafness but no renal impairment. Approximately 28.6% of patients with HDR syndrome have these two abnormalities only without renal involvement (3). Hypoparathyroidism in HDR results in hypocalcaemia, which may be asymptomatic or present with muscle aches/spasms, neuromuscular irritability, seizures or tetany.

Hypocalcaemia is a rare but well documented cause of optic disc oedema. Presentation of patients to eye clinic with hypocalcaemia-induced optic disc oedema is uncommon and this may contribute to delays in making a diagnosis. To the best of our knowledge, this may be the first case of HDR syndrome diagnosed following presentation with hypocalcaemia-induced optic disc oedema.

Disc swelling in patients with hypocalcaemia may be due to increased intracranial pressure (papilloedema) or as a result of disruption of axoplasmic flow secondary to low calcium in patients with no evidence of intracranial hypertension (1). Low calcium levels may lead to hypersecretion of cerebrospinal fluid (secondary to an increase in choroid plexus adenylate cyclase activity) leading to the former neuro-ophthalmic presentation whereas the latter presentation may lead to ischaemic optic neuropathy. It is therefore important that clinicians are aware of this rare cause of optic disc oedema so that serum calcium levels are assessed at the point when patients are being referred to the medical team for further neurological investigations. Although the diagnosis in our patient was made quite quickly once he was referred by the ophthalmology team, one case report highlighted the risk of performing expensive and invasive investigations if serum calcium is not checked earlier on in the work up to reach a diagnosis (1). In fact, our patient had been reviewed 10 years previously and treated for raised intracranial pressure (despite normal opening CSF opening pressures) which, in retrospect, may possibly have been hypocalcaemia-induced optic disc oedema.

HDR syndrome has been shown to be genotypically heterogeneous (4). Our patient harboured a GATA3 gene mutation confirmed on genetic studies whereas deletions in chromosome 10p 14 can also cause the syndrome. In our patient who had hypoparathyroidism- induced hypocalcaemia, it was important for a genetic cause to be considered. On review of previous pathology results, there was evidence of persistently low calcium level. This, in combination with a history of deafness and family history of hypocalcaemia and renal impairment, raised suspicions to an underlying syndrome.

The genetic diagnosis has led to the diagnosis of HDR in the aforementioned family members.

Conclusion

Hypocalcaemia- induced disc oedema is uncommon but can be the presenting feature of HDR syndrome. Patients observed in eye clinic with features of optic nerve disc oedema should have serum calcium measured. Furthermore, patients with hypoparathyroidism-associated hypocalcaemia should have a personal and family history of deafness and renal dysfunction explored as this may lead to the diagnosis of HDR syndrome.

Declaration

The authors declare that they have no conflict of interest. No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article

Acknowledgments

The patient in this manuscript has given a written informed consent to the publication of his clinical case details.

References

1. Abu-Ain, M., Aazem, S., Morton, C., Kumwenda, M., Griffiths, D., & Jacob, A. (2010). A rare potentially treatable cause of bilateral optic disc swelling. *BMJ case reports, 2010*, bcr0320102835. https://doi.org/10.1136/bcr.03.2010.2835

2. Sforza, G., Deodati, A., Moavero, R., Papetti, L., Frattale, I., Vigevano, F., Cianfarani, S., & Valeriani, M. (2022). Benign Intracranial Hypertension Due to Hypoparathyroidism: A Case Report. *Frontiers in neurology*, *12*, 818638. https://doi.org/10.3389/fneur.2021.818638

3. Joseph, A., Sirisena, N. D., Kumanan, T., Sujanitha, V., Strelow, V., Yamamoto, R., Wieczorek, S., & Dissanayake, V. (2019). Hypoparathyroidism, Sensorineural deafness and renal disease (Barakat syndrome) caused by a reduced gene dosage in GATA3: a case report and review of literature. *BMC endocrine disorders*, *19*(1), 111. https://doi.org/10.1186/s12902-019-0438-4

4. Barakat, A. J., Raygada, M., & Rennert, O. M. (2018). Barakat syndrome revisited. *American journal of medical genetics. Part A*, *176*(6), 1341–1348. https://doi.org/10.1002/ajmg.a.38693