Expanding the phenotypic spectrum of HDR (Barakat) syndrome shows a possible link between GATA3 mutation and Autoimmune disorders including Type 1 Diabetes

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Introduction

- HDR (Hypoparathyroidism, Deafness, and Renal anomalies) syndrome is a rare autosomal dominant disorder caused by GATA3 haploinsufficiency [1].
- While typically defined by its classical triad, very few associated autoimmune conditions have been described in the literature. We report two siblings with features of HDR syndrome and Type 1 Diabetes Mellitus, expanding the phenotypic spectrum of this condition [2,3].

GATA3 Scientific Literature

- Although the precise prevalence of HDR syndrome remains uncertain, it is widely acknowledged as an exceedingly rare condition.
- To the best of our knowledge, only 191 cases of HDR syndrome have been documented in the scientific literature thus far. The initial documentation of HDR syndrome dates back to 1977, when cases were identified in an American family (Hasegawa et al., 1997) [3].
- The genetic basis of this disorder was linked to mutations in the *GATA3* gene, which is located on chromosome 10p14 and encodes a dual zinc-finger transcription factor.
- GATA3 is critical for the development of various tissues, including the parathyroid gland, the sensory components of the auditory system, and the kidneys. It is also essential for the development and function of the immune system, though very few clinical autoimmune conditions have been described in the literature.

Case study

Patient 1:

- A 14-year-old girl, who has congenital sensorineural deafness, was diagnosed with Hypoparathyroidism with low serum calcium and raised phosphate with inappropriately low parathyroid hormone.
- A renal ultrasound revealed an absent right kidney with a compensatory hypertrophied left kidney, confirming HDR triad clinically.
- At the age of 6 years, she was diagnosed with Type 1 diabetes, when

she was in DKA with HbA1c 14% and positive GAD antibodies. She had negative IA2 antibodies.

Patient 2:

- A 6-year-old sister with congenital sensorineural deafness and unilateral ptosis.
- Presented with osmotic symptoms and was diagnosed with Type 1 Diabetes (HbA1c 7.9%), without ketoacidosis.
- Positive GAD, IA2, and Coeliac TTG IgA antibodies.
- She has low-normal calcium and parathormone and no renal anomalies detected on Ultrasound scan.

Family history

- Family history revealed consanguineous parents; the mother and a brother had congenital deafness, but no diabetes.
- The brother carried a *GATA3* mutation, supporting a diagnosis of HDR syndrome in the four family members.

Investigations

Laboratory	Patient 1	Patient 2
HbA1c	> 14 %	7.9 %
Pancreatic auto-antibodies	Positive GAD only	Positive both GAD and IA2
TTG IgA antibody	Negative	Positive
PTH (pmol/L)	1.07 (low)	3.57
Calcium (mmol/L)	1.78 (low)	2.16 (low)
Phosphate (mmol/L)	1.81 (high)	1.68

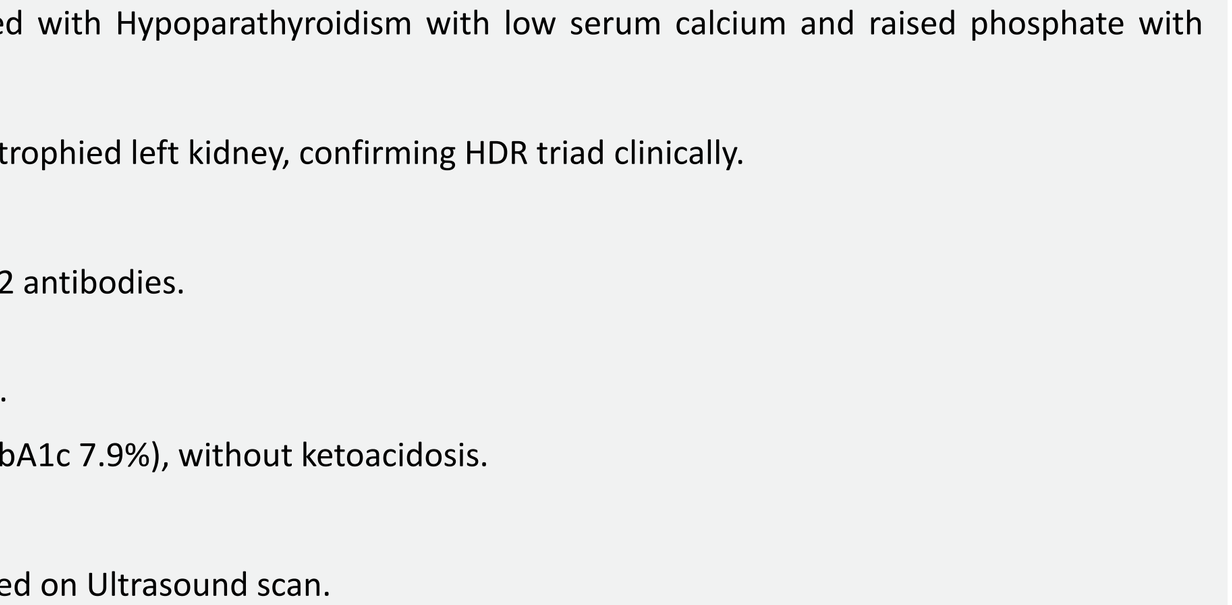

Figure1: GATA-3 Function in Innate and Adaptive Immunity

Conclusion

- These cases highlight a potential link between GATA3 mutations and autoimmune dysregulation.
- GATA3 influences immune pathways and is expressed in pancreatic β-cells, suggesting a mechanistic basis for T1DM susceptibility.
- Clinicians should consider HDR syndrome in children with T1DM and co-existing deafness or renal abnormalities and monitor serum calcium level in these situation.
- Further study is needed to clarify the role of GATA3 in immune-mediated diseases like Type 1 Diabetes and Coeliac disease.

References

1. *Van Esch, H., Groenen, P., Nesbit, M. et al. GATA3 haplo-insufficiency causes human HDR syndrome. Nature 406, 419–422 (2000).*
2. *Characterisation of GATA3 Mutations in the Hypoparathyroidism, Deafness, and Renal Dysplasia (HDR) Syndrome Nesbit, M. Andrew et al. Journal of Biological Chemistry, Volume 279, Issue 21, 22624 - 22634*
3. *A GATA3 gene mutation that causes incorrect splicing and HDR syndrome: a case study and literature review Sec. Genetics of Common and Rare Diseases Volume 14 – 2023*
4. *Neufeld M, MacLaren N, Blizzard R. Autoimmune polyglandular syndromes. Pediatric annals. 1980 Apr 1;9(4):43-53.*

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