Unusual Association of Pancreatic Islet Cell Hyperplasia and CYP1B1 Homozygous Gene Variant in a 12-Year-Old Child

Aws H. AL-Numan*
***Department of Pediatrics, College of Medicine, University of Mosul, Mosul, Iraq**
Correspondence: awshazimah72@uomosul.edu.iq

(Ann Coll Med Mosul 2025; 47 (2):259-261).
Received: 27th April 2025; Revised 3rd May 2025; Accepted: 13th May 2025.

ABSTRACT

Background: The CYP1B1 gene is typically associated with congenital glaucoma and certain cancers, but its role in metabolic regulation remains less understood. We report a case that suggests a possible new connection between CYP1B1 mutations and pancreatic islet cell hyperplasia.

Case Presentation: Our patient, a 12-year-old boy with a known history of congenital glaucoma and familial Mediterranean fever (FMF), presented with recurrent hypoglycemic episodes initially thought to be seizures due to epilepsy. Further workup revealed high insulin levels during these episodes. A PET/CT scan eventually identified a lesion in the pancreas, and surgery confirmed islet cell hyperplasia. Following resection, his hypoglycemic episodes resolved. Genetic testing revealed a homozygous mutation in CYP1B1, along with a known MEFV variant linked to FMF.

Discussion: This appears to be the first reported case linking a CYP1B1 mutation to islet cell hyperplasia. One theory is that the gene's role in hormone and lipid metabolism, as well as oxidative stress regulation, may influence β-cell activity. Chronic inflammation from FMF could have also contributed to pancreatic stress or compensatory hyperplasia.

Conclusion: This unusual case raises important questions about the metabolic roles of CYP1B1. It also highlights the value of genetic testing in unexplained cases of hyperinsulinemic hypoglycemia, especially in patients with complex medical histories.

Keywords: CYP1B1, FMF, congenital glaucoma, Pancreatic Islet Cell Hyperplasia, hypoglycemia

ارتباط غير معتاد بين تضخم خلايا جزر البنكرياس والمتغير الجيني المتجانس CYP1B1 لدى طفل يبلغ من العمر ١٢ عاما

اوس حازم النعمان*
*فرع طب الاطفال ، كلية الطب ، جامعة الموصل ، الموصل ، العراق

الخلاصة

الخلفية: يرتبط جين CYP1B1 بشكل أساسي بالزرق الخلقي وبعض الأورام الخبيثة، إلا أن دوره في التنظيم الأيضي لا يزال غير واضح بشكل كامل. نقدم في هذا التقرير حالة سريرية تشير إلى احتمال وجود ارتباط جديد بين طفرات CYP1B1 وفرط تنسج خلايا الجزر البنكرياسية.

عرض الحالة: مريضنا طفل يبلغ من العمر ١٢ عامًا، لديه تاريخ مرضي معروف بالإصابة بالزرق الخلقي وحمى البحر الأبيض المتوسط العائلية (FMF)، حضر بشكاية من نوبات نقص سكر دم متكررة، والتي اعتُقد في البداية أنها نوبات صرعية ناجمة عن الصرع. أظهرت الفحوصات المخبرية خلال النوبات ارتفاع مستويات الإنسولين. لاحقًا، كشفت صورة PET/CT عن وجود آفة ضمن البنكرياس، وتم تأكيد تشخيص فرط تنسج خلايا الجزر البنكرياسية جراحيًا. بعد الاستئصال الجراحي للآفة، اختفت نوبات نقص سكر الدم. أظهر التحليل الجيني وجود طفرة متماثلة اللواقح في جين CYP1B1، بالإضافة إلى وجود متغير معروف في جين MEFV المرتبط بمرض حمى البحر الأبيض المتوسط العائلية.

الكلمات المفتاحية: حمى البحر الابيض المتوسط ، الزرق الخلقي، تضخم خلايا جزر البنكرياس، انخفاض السكر في الدم، CYP1B1.

INTRODUCTION

CYP1B1 gene mutations are well-known causes of primary congenital glaucoma and eventual vision loss due to increased intraocular pressure and optic nerve damage if not treated early. This gene has also been implicated in the development of cancers in various organs, including the ovaries, uterus, prostate, colon, lungs, and brain, as the CYP1B1 enzyme is involved in the detoxification of procarcinogens [1,2].

Additionally, CYP1B1 plays a role in metabolic pathways related to steroid hormones, vitamins, fatty acids, and other substances, suggesting a potential future application in treating metabolic disorders through genetic modulation [3].

However, a link between this mutation and pancreatic islet cell hyperplasia with hyperinsulinemia has not previously been reported.

Case Presentation

A 12-year-old male with a history of bilateral congenital glaucoma and familial Mediterranean fever (FMF) presented with recurrent episodes of seizures and loss of consciousness due to severe hypoglycemia. Initially misdiagnosed with idiopathic epilepsy, he was treated with sodium valproate, which provided only partial relief.

Critical blood sampling during hypoglycemic episodes revealed persistent hyperinsulinemia. The severity of the episodes necessitated repeated hospitalizations and treatment with hypertonic dextrose and subcutaneous octreotide. Initial imaging was unremarkable, but a PET/CT scan revealed a hypodense, solitary, non-FDG avid lesion at the neck of the pancreas.

A partial pancreatectomy with splenectomy was performed to remove the suspected insulinoma. Pathology results revealed hyperplasia of the islets of Langerhans. Postoperatively, the hypoglycemic episodes resolved.

Past Medical History

In addition to congenital glaucoma, the patient experienced persistent high fevers and recurrent abdominal pain from infancy. Prior to an FMF diagnosis, he underwent an appendectomy during an acute episode. Subsequently, he developed recurrent intestinal obstructions requiring multiple exploratory surgeries for adhesion release.

After confirming FMF via genetic testing, the patient began colchicine therapy (1 mg daily) with limited response. Increasing the dose led to significant gastrointestinal side effects, including nausea and vomiting. He also suffered from recurrent, painful arthritis affecting the hips and knees, typically lasting 7–10 days and accompanied by high fevers.

There were no resulting deformities or functional impairments.

Due to inadequate response to colchicine, infliximab (5 mg/kg every two months after induction doses at weeks 0, 2, 6, and 14) was initiated, along with weekly subcutaneous methotrexate. The patient showed partial improvement, and a plan was made to administer infliximab every six weeks to better control FMF symptoms.

Genetic Evaluation

Following the diagnosis of FMF, whole exome sequencing was conducted to explore a potential genetic basis for the patient's hyperinsulinemia. The results revealed a homozygous CYP1B1 gene mutation and a homozygous variant in the MEFV gene.

DISCUSSION AND CONCLUSION

Pancreatic islet cell hyperplasia, or nesidioblastosis, is a rare condition more commonly seen in infants and young children, occasionally affecting adults. It often leads to hyperinsulinemia and hypoglycemia. Known genetic causes include mutations in ABCC8, KCNJ11, HADH1, GK, GLUD1, SLC16A1, UCP2, and HNF4A, although approximately 50% of cases remain idiopathic [4,5]. CYP1B1 overexpression has been associated with cancers in hormone-sensitive tissues such as the breast, ovary, endometrium, and prostate, because CYP1B1 plays a role in breaking down both pro-carcinogens and estrogen, polymorphisms and mutations could affect how the enzyme works, which might increase the risk of hormone-related cancers [6].

To our knowledge, an association between CYP1B1 mutations and islet cell hyperplasia has not been previously reported. One possible explanation in this case is that CYP1B1 dysfunction disrupts steroid hormone and fatty acid metabolism, leading to abnormal β-cell stimulation, oxidative stress imbalance in pancreatic tissues, and altered insulin gene expression. Similar mechanisms have been observed in estrogen-dependent carcinogenesis due to the enzyme's role in metabolizing estradiol and estrone into DNA-damaging catechol estrogens [7]. Research by Tang Y. et al. demonstrated that cells lacking CYP1B1 experienced elevated oxidative stress, which was reversible with antioxidant treatment, highlighting the enzyme's role in maintaining redox balance. In the context of pancreatic islet cells-known to be particularly sensitive to oxidative damage due to limited antioxidant defenses-dysregulated CYP1B1 activity could disrupt this delicate balance.

This oxidative stress may impair β-cell function or trigger compensatory mechanisms such as islet cell hyperplasia, offering a plausible mechanistic link between CYP1B1 dysfunction and the patient's observed endocrine abnormality [8].

Another potential contributing factor could be chronic systemic inflammation associated with FMF. Inflammatory cytokines such as TNF-α and IL-1 are known to influence β-cell function and could induce pancreatic stress or compensatory hyperplasia [9,10].

This case highlights a rare and previously unreported association that may pave the way for further investigation into the metabolic effects of CYP1B1 mutations. Genetic evaluation should be considered in unexplained cases of hyperinsulinemic hypoglycemia.

Funding

No financial support was received from any institution or organization for the preparation or submission of this review.

Conflicts of Interest

The authors declare that there are no financial or personal relationships that could have influenced the work reported in this manuscript.

Ethical Approval

Ethical approval does not apply to this article as it does not involve original research on human or animal subjects, or any identifiable patient information.

REFERENCES

1. Alsubait A, Aldossary W, Rashid M, Algamdi A, Alrfaei BM. CYP1B1 gene: Implications in glaucoma and cancer. Journal of Cancer. 2020;11(16):4652–61. Doi:10.7150/jca.42669.
2. Dąbrowski A, Nowicki M, Budzyńska A, Suchodolski J, Ogórek R, Chabowski M, et al. Analysis of CYP1B1 Polymorphisms in Lung Cancer Patients Using Novel, Quick and Easy Methods Based on CAPS and ACRS-PCR Techniques. Int J Mol Sci. 2024;25(12):6676. Doi: 10.3390/ijms25126676.
3. Li F, Zhu W, Gonzalez FJ. Potential role of CYP1B1 in the development and treatment of metabolic diseases. Pharmacol Ther. 2017;178:18–30. Doi: 10.1016/j.pharmthera.2017.03.007.
4. Thompson, Michael J. Mordes, John P. (2015). Hypoglycemia in Pancreatic Disease.Pancreapedia: Exocrine Pancreas Knowledge Base, Doi: 10.3998/panc.2015.11.
5. Palladino AA, Stanley CA. Nesidioblastosis No Longer! It's All about Genetics. J Clin Endocrinol Metab. 2011;96(3):617–9. Doi: 10.1210/jc.2011-0164.
6. Gajjar K, Martin-Hirsch PL, Martin FL. CYP1B1 and hormone-induced cancer. Cancer Letters. 2012 Nov 1-321(1):1-9. doi: 10.1016/j.canlet.2012.04.021. Epub 2012 May 2. Doi: 10.1016/j.canlet.2012.02.001
7. Liehr JG. Is estradiol a genotoxic mutagenic carcinogen? Endocr Rev. 2000;21(1):40–54. Doi: 10.1210/edrv.21.1.0386.
8. Tang Y, Scheef EA, Wang S, Sorenson CM, Marcus CB, Jefcoate CR, Sheibani N. "CYP1B1 expression promotes the proangiogenic phenotype of endothelium through decreased intracellular oxidative stress and thrombospondin-2 expression." Blood. 2009;113(3):744–754. Doi: 10.1182/blood-2008-03-145219.
9. Donath MY, Størling J, Maedler K, Mandrup-Poulsen T. Inflammatory mediators and islet beta-cell failure: a link between type 1 and type 2 diabetes. J Mol Med. 2003;81(8):455–70. Doi: 10.1007/s00109-003-0450-y.
10. Eizirik DL, Colli ML, Ortis F. The role of inflammation in insulitis and beta-cell loss in type 1 diabetes. Nat Rev Endocrinol. 2009;5(4):219–26. Doi: 10.1038/nrendo.2009.21