Section: Internal Medicine

Case Report

A NEVER-REPORTED TRIAD: WILLIAMS–BEUREN SYNDROME, MAN1B1 GENE MUTATION AND NON-CIRRHOTIC PORTAL HYPERTENSION

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Received : 05/02/2026
Received in revised form : 29/03/2026
Accepted : 15/04/2026

Keywords:
MAN1B1, MAN1B1 mutation, NCPF, williams-beuren syndrome, williams syndrome.

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DOI: 10.47009/jamp.2026.8.3.22

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (3); 125-128

ABSTRACT

We report an unusual case of an 18-year-old male with genetically confirmed Williams–Beuren syndrome and concurrent MAN1B1 mutation presenting with features of Non-cirrhotic portal hypertension and spontaneous intrahepatic portosystemic shunting. Williams–Beuren syndrome is classically associated with elastin arteriopathy and supravalvular aortic stenosis, while MAN1B1 mutations are linked to intellectual disability, truncal obesity, and dysmorphism. The patient demonstrated portal hypertension with preserved liver function and absence of cirrhosis, consistent with non-cirrhotic portal fibrosis phenotype. Current literature does not establish any pathogenic or causal relationship between Williams–Beuren syndrome, MAN1B1 mutation, and non-cirrhotic portal hypertension. This case highlights a previously unreported clinical association and expands the phenotypic spectrum of these rare genetic disorders, warranting further investigation into possible shared vascular or connective tissue mechanisms.

INTRODUCTION

Williams-Beuren syndrome (WBS) is a multisystem disorder characterized by a microdeletion on chromosome 7q11.23 (elastin gene), supravalvular aortic stenosis, other vascular abnormalities, distinctive facial features, hypercalcemia, bone defects and a unique neurobehavioral profile.[1] The vascular pathology in Williams syndrome is well described and primarily attributed to elastin arteriopathy, leading to arterial stenoses of varying severity.[2]

The MAN1B1 gene is located on chromosome 9q34.3 and comprises 13 exons. It encodes the protein endoplasmic reticulum mannosyl-oligosaccharide 1,2-alpha-mannosidase (ERManI) that is found to play an important role in the disposal of misfolded glycoproteins.[3] The phenotype associated with MAN1B1 mutations includes mild to moderate ID, truncal obesity, muscular hypotonia and modest dysmorphic features (broad nasal bridge, prominent nose, thin upper lip, curved eyebrows)

Non-cirrhotic portal hypertension (NCPH), particularly non-cirrhotic portal fibrosis (NCPF), is an important cause of portal hypertension in the pediatric age group and adolescents.[4] It is characterized by features of portal hypertension such as splenomegaly and hypersplenism, in the absence of cirrhosis and with preservation of liver function.[5] There is no causal link between elastin arteriopathy and NCPH in the current literature. There is also no causal link between the causation of NCPH due to MAN1B1 gene mutations. And there is no correlating pathogenesis between WBS and MAN1B1 gene. Therefore, there is no established link connecting Williams- Beuren syndrome, MAN1B1 gene, and non-cirrhotic portal hypertension in the literature. We report a rare case of an 18-year-old male with genetically confirmed Williams-Beuren syndrome and MAN1B1 gene mutation with features of non-cirrhotic portal hypertension with spontaneous intrahepatic portosystemic shunting, highlighting a previously unreported clinical association.

Case Presentation

An 18-year-old male was referred to our centre for evaluation of massive splenomegaly detected at a peripheral facility. He initially reported a history of low-grade intermittent fever for three days, which had subsided one day prior to presentation. There was no history of abdominal pain, gastrointestinal bleeding (hematemesis, melena, or bleeding per rectum), jaundice, or prior episodes suggestive of decompensated liver disease.

A notable behavioural history of increased adamant and impulsive tendencies was present, for which he

ISSN (O): 2687-5365; ISSN (P): 2753-6556

was a known case of attention-deficit/hyperactivity disorder on atomoxetine therapy. His past medical history was significant for a suspected diagnosis of PJS, based on prior clinical evaluation. He had a solitary recital polyp and biopsy showed an arborizing pattern. Family history was unremarkable, with no similar illnesses reported.

On examination, the patient was hemodynamically stable. Dysmorphic facial features were noted, characterized by a broad forehead, periorbital fullness, and a wide mouth [Figure 1]. Cardiovascular examination revealed an ejection systolic murmur best heard in the aortic area. Abdominal examination demonstrated massive splenomegaly, corresponding to Hackett grade IV, extending well below the left costal margin. There was no clinical evidence of ascites or hepatomegaly. The remainder of the systemic examination was unremarkable.

FIGURE 1: Suspected "Elfin" facies in the patient charecterized by broad nasal bridge, prominent nose, thin upper lip, curved eyebrows

Table 1: The laboratory investigations were as follows

Investigation	Value	Reference Range
Hemoglobin	**10.8 g/dL**	**13–17 g/dL**
Total Leukocyte Count	2,700 cells/mm³	4,000–11,000 cells/mm³
Platelet Count	70,000 cells/mm³	150,000–400,000 cells/mm³
MCH	28.9 pg	27–33 pg
RDW	18.2%	11.5–14.5%
PDW	22.4%	9–17%
Absolute Neutrophil Count	1.4 $\times 10^9$ /L	2.0–7.0 $\times 10^9$ /L
Absolute Lymphocyte Count	0.9 $\times 10^9$ /L	1.0–3.0 $\times 10^9$ /L
Peripheral Blood Smear	Anisopoikilocytosis with microcytic and normocytic RBCs (bimorphic anemia)	—
Liver Function Tests	Within normal limits	—
Renal Function Tests	Within normal limits	—
ANA	Negative	Negative

TABLE 1: Laboratory investigations done for the patient
MCH - Mean corpuscular hemoglobin
RDW - Red cell distribution width
PDW - Platelet distribution width
ANA - Anti-nuclear antibody

Ultrasound Doppler evaluation of the portal system demonstrated splenomegaly (approximately 15 cm) with dilated splenic (10 mm) and mesenteric veins (9 mm), along with the presence of splenorenal collaterals, suggestive of portal hypertension. Altered hepatic echotexture prompted further imaging, which revealed a spontaneous intrahepatic portosystemic shunt. Transthoracic echocardiography identified supravalvular aortic stenosis at the level of sinotubular junction 17 mm from aortic annulus [Figure 2].

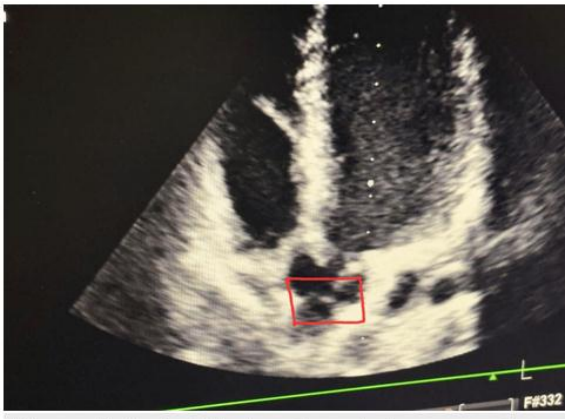


Figure 2: Apical 5 chambered view revealing a supravalvular aortic stenosis at the level of

In view of the constellation of findings-including dysmorphic facies, vascular abnormalities, and behavioral phenotype-genetic evaluation was pursued. Esophago Gastro Duodenoscopy and Colonoscopy was done for this patient in view of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

previous documentation of a rectal polyp with a possibility of Peutz Jeghers syndrome, however the findings were normal. FibroScan of liver showed a 4.4 Kpa liver stiffness (within normal limits). CECT abdomen suggestive of moderate splenomegaly with spontaneous intrahepatic portosystemic shunt. No features suggestive of Chronic liver disease seen [Figure 3].

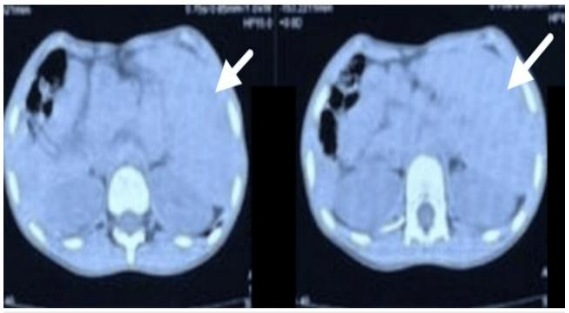


FIGURE 3: CECT slices showing moderate splenomegaly

Genetic analysis was done which was suggestive of variants in MAN1B1 gene and RET gene. Patient had no features of Multiple Endocrine Neoplasia type IIB and investigations for the same were inconsistent with MEN2B. A clinical diagnosis of NCPH with hypersplenism, in the setting of WBS and MAN1B1 gene mutation, was made. The patient was initiated on non-selective beta-blocker therapy (propanolol) for portal hypertension and managed conservatively with planned surveillance for NCPF and MEN2B.

DISCUSSION

Williams-Beuren syndrome (WBS) and non-cirrhotic portal hypertension (NCPH) are individually well-described clinical entities with distinct pathophysiological bases. WBS is primarily a disorder of elastin arteriopathy affecting medium- and large-sized arteries, MAN1B1 gene mutations are associated with intellectual disability and dysmorphic facies while NCPH represents a vascular disorder of the portal system in the absence of cirrhosis. The coexistence of these three conditions in a single patient raises questions regarding possible shared vascular or developmental mechanisms, although such associations have not been previously established.

The vascular involvement in WBS is well documented, with elastin gene deletion leading to arterial stiffness, luminal narrowing, and altered vascular compliance. While this typically manifests as supravalvular aortic stenosis and other large-vessel abnormalities, involvement of cerebral vasculature has also been reported, such as in association with Moyamoya disease.[6] Neurobehavioral manifestations, including attention-deficit/hyperactivity disorder, are also frequently observed in WBS and have been linked to underlying neurodevelopmental and genetic mechanisms.[7]

However, despite the systemic nature of elastin arteriopathy, portal venous system involvement has not been described in the literature. To date, there is no evidence linking Williams Beuren syndrome and MAN1B1 gene mutation to portal hypertensive states such as NCPH or to congenital vascular anomalies involving the portal system.

NCPH, particularly in the form of non-cirrhotic portal fibrosis, is understood to arise from obliterative portal venopathy and altered intrahepatic vascular resistance. While various etiologies including infections, prothrombotic states, and environmental exposures have been implicated, its association with defined genetic syndromes remains limited. Vascular developmental disorders, such as Adams-Oliver syndrome, have been described with systemic vascular anomalies,[8] but even in such conditions, involvement of the portal venous system is not consistently observed, and no direct parallels to WBS or MAN1B1 mutation have been established.

Taken together, the available literature highlights that while WBS, MAN1B1 gene and certain vascular or developmental disorders may independently demonstrate multisystem involvement, there is currently no established pathophysiological or clinical link connecting these entities. The overlap observed in our patient-encompassing elastin arteriopathy, dysmorphic facies due to MAN1B1 gene mutation, and portal hypertension with intrahepatic shunting-appears to be unprecedented.

To the best of our knowledge, this is the first reported case describing the coexistence of WBS, MAN1B1 gene mutation, and NCPH with spontaneous intrahepatic portosystemic shunting. This case expands the phenotypic spectrum of WBS and MAN1B1 mutation raising the possibility of previously unrecognized vascular involvement of the portal system. A notable limitation in the evaluation of this patient was restricted consent from the caregiver, which precluded comprehensive diagnostic workup and documentation of certain imaging findings, thereby limiting the extent of clinical correlation and completeness of recorded data.

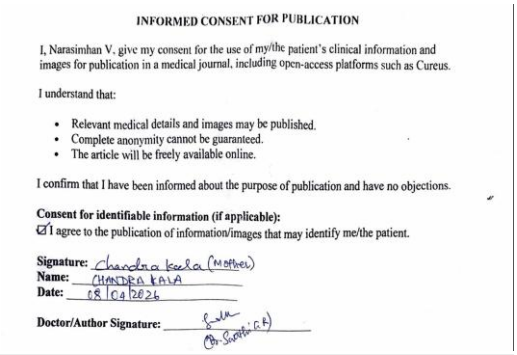
CONCLUSION

This case describes a previously unreported coexistence of Williams-Beuren syndrome, MAN1B1 gene mutation, and non-cirrhotic portal hypertension with spontaneous intrahepatic portosystemic shunting. In the absence of cirrhosis or other identifiable etiologies, the findings suggest a possible extension of vascular involvement beyond the classical arterial manifestations of WBS. The overlap of dysmorphic, neurobehavioral, and vascular features highlights the diagnostic complexity and underscores the importance of comprehensive evaluation in patients with multisystem genetic disorders presenting with portal hypertension.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

From a future perspective, this observation raises the possibility of previously unrecognized shared developmental or vascular mechanisms linking these conditions. Further studies, including larger case series and genetic analyses, are needed to explore potential associations and clarify underlying pathophysiology. Improved recognition of such atypical presentations may aid in earlier diagnosis, targeted surveillance, and better risk stratification.

Appendices



INFORMED CONSENT FOR PUBLICATION

I, Narasimhan V, give my consent for the use of my/the patient's clinical information and images for publication in a medical journal, including open-access platforms such as Cureus.

I understand that:

- Relevant medical details and images may be published.
- Complete anonymity cannot be guaranteed.
- The article will be freely available online.

I confirm that I have been informed about the purpose of publication and have no objections.

Consent for identifiable information (if applicable):
☑ I agree to the publication of information/images that may identify me/the patient.

Signature: Chandra kala (Mother)
Name: CHANDRA KALA
Date: 08/04/2026

Doctor/Author Signature:

FIGURE 4: Consent form signed by the patient's mother (The legally appointed

The consent form for the publication of patient's details was taken [Figure 4].

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Yogesh S, Preeti N, Srihari N, Sahasyaa Adalarasan, Swathi G R, Jayaprakash N, Hariharan C

Acquisition, analysis, or interpretation of data: Yogesh S, Preeti N, Srihari N, Sahasyaa Adalarasan, Swathi G R, Jayaprakash N, Hariharan C

Drafting of the manuscript: Yogesh S, Preeti N, Srihari N, Sahasyaa Adalarasan, Swathi G R, Jayaprakash N, Hariharan C

Critical review of the manuscript for important intellectual content: Yogesh S, Preeti N, Srihari N, Sahasyaa Adalarasan, Swathi G R, Jayaprakash N, Hariharan C

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556