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METABOLIC AND HEMATOLOGIC CONVERGENCE: A RARE CASE OF CONCURRENT GLYCOGEN STORAGE DISORDER TYPE III AND FACTOR XIII DEFICIENCY

Enzymatic Crossroads: Unravelling the Biochemical Basis of Dual Deficiencies in Debranching Enzyme and Transglutaminase

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Abstract: Glycogen Storage Disorder Type III (GSD III) and Factor XIII deficiency are individually rare genetic disorders with distinct biochemical pathways. We report an unprecedented case of their coexistence in an 11-year-old female born to consanguineous parents. This case highlights the critical role of comprehensive biochemical evaluation in diagnosing complex presentations involving multiple metabolic pathways.

INTRODUCTION

Glycogen Storage Disorder Type III results from deficiency of the glycogen debranching enzyme (amylo-1,6-glucosidase), causing abnormal glycogen accumulation in liver, muscle, and heart. Factor XIII deficiency is a rare bleeding disorder caused by deficient transglutaminase activity, which impairs fibrin cross-linking during clot formation. The biochemical intersection of these disorders presents unique diagnostic challenges requiring sophisticated laboratory analysis.

CASE PRESENTATION

An 11-year-old female born to consanguineous parents presented with a complex clinical picture. Her early history included hypoglycaemic seizures, abdominal distension, and delayed motor development at age 2. By age 4, she developed epistaxis that worsened with age. From age 7, she experienced recurrent hypoglycaemic episodes.

Physical examination revealed significant hepatomegaly with liver palpable 12 cm below the right costal margin. The liver span measured 17 cm, with smooth, non-tender edges. Other systems were clinically normal.

BIOCHEMICAL AND LABORATORY INVESTIGATIONS

Haematological Parameters:

Parameter	Patient's Value	Reference Range
Haemoglobin	11 g/dL	11.5-15.5 g/dL
WBC	14,000/µL	4,500-13,500/µL
Platelet count	400,000/µL	150,000-450,000/µL
Blood smear	Normocytic and normochromic	

Liver Function Parameters:

Parameter	Patient's Value	Reference Range
Total Bilirubin	0.26 mg/dL	0.1 - 1.0 mg/dL
Direct Bilirubin	0.12 mg/dL	0.0 - 0.3 mg/dL
Alkaline Phosphatase	314 U/L	150 – 420 U/L
Alanine Transaminase	244 U/L	7 - 35 U/L
Aspartate Transaminase	302 U/L	15 - 40 U/L
Gamma Glutamyl Transferase	58 U/L	5 – 25 U/L
Serum Albumin	4.1 g/dL	3.5 – 5.0 g/dL
Serum Globulin	3.6 g/dL	2.3 – 3.5 g/dL

Metabolic Parameters:

Parameter	Patient's Value	Reference Range
Fasting blood sugar	69 mg/dL	70-100 mg/dL
Blood urea	30 mg/dL	15-36 mg/dL
Serum creatinine	0.6 mg/dL	0.3-0.7 mg/dL
Serum uric acid	4.2 mg/dL	2.5-5.5 mg/dL

Coagulation Parameters:

Parameter	Patient's Value	Reference Range	Impression
Factor XIII activity	40.2%	70-140%	Decreased (mild deficiency)
Von Willebrand antigen	120%	50-160%	Normal

Whole Exome and Mitochondrial Sequencing:

Gene Transcript	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
AGL (+) (ENST00000361915.2	Exon 22	c.2816T (p.Leu939Ter)	Homozygous	Glycogen storage disease IIIa (OMIM#232400) Glycogen storage disease IIIb (OMIM#232400)	Autosomal recessive	Likely pathogenic (PVS1,PM2)

Specialized Biochemical Testing:

- Enzyme assays for acid sphingomyelinase and β-glucosidase: Normal (ruling out Niemann-Pick disease)
- Liver biopsy: Mild swollen hepatocytes with vacuolated cytoplasm
- PAS staining: Positive (confirming glycogen accumulation)
- Platelet surface glycoprotein receptor analysis: Normal
- Platelet aggregometry: Normal

BIOCHEMICAL SIGNIFICANCE AND DIAGNOSTIC APPROACH

GSD III Biochemical Pathophysiology: The patient's presentation of hepatomegaly, hypoglycaemia, and PAS-positive liver biopsy suggested abnormal glycogen metabolism. Liver function tests revealed markedly elevated transaminases (ALT 244 U/L, AST 302 U/L) and GGT (58 U/L), reflecting hepatocellular damage from glycogen accumulation. Whole exome sequencing confirmed a homozygous nonsense mutation in the AGL gene (c.2816T>A; p.Leu939Ter) in exon 22, classified as likely pathogenic (PVS1, PM2). GSD III involves deficient debranching enzyme activity, leading to accumulation of abnormally structured glycogen with short outer branches. This biochemical defect results in:

1. Impaired glycogenolysis causing hypoglycaemia (patient's fasting glucose: 69 mg/dL)
2. Hepatomegaly due to glycogen accumulation (liver span 17 cm)
3. Elevated liver enzymes from hepatocyte damage (ALT 244 U/L, AST 302 U/L)
4. Positive PAS staining confirming glycogen deposition

Factor XIII Deficiency Biochemical Basis: Despite normal routine coagulation tests (PT, aPTT, INR), the patient's epistaxis warranted specific factor assays. Factor XIII (transglutaminase) is essential for stabilizing fibrin clots through cross-linking. The biochemical significance of Factor XIII deficiency includes:

1. Normal initial clot formation but impaired clot stability
2. Undetectable in routine coagulation tests, requiring specific activity assays
3. Activity level of 40.2% indicating mild deficiency sufficient to cause mucosal bleeding

Biochemical Correlation with Clinical Presentation: The dual enzymatic deficiencies elegantly explain the patient's complex presentation:

- Hypoglycaemic episodes: Defective glycogenolysis due to debranching enzyme deficiency
- Hepatomegaly: Accumulation of abnormal glycogen in liver
- Epistaxis: Impaired fibrin cross-linking due to Factor XIII deficiency
- Delayed motor development: Possible muscle involvement in GSD III
- Genetic confirmation: Homozygous pathogenic AGL variant definitively establishing GSD III diagnosis

MANAGEMENT BASED ON BIOCHEMICAL UNDERSTANDING

Treatment was tailored to address both enzymatic deficiencies:

1. Cornstarch diet: Provides slow-release glucose to prevent hypoglycaemia
2. Fructose restriction: Reduces substrate load for alternative metabolic pathways
3. Frequent feeds: Maintains glucose homeostasis
4. Tranexamic acid (10 mg/kg/dose): Stabilizes clots by inhibiting fibrinolysis
5. Regular monitoring: Monthly liver function tests and biannual Factor XIII activity assays

DISCUSSION

This case illustrates the critical importance of biochemical testing in diagnosing complex presentations. The initial differential diagnoses included Wilson's disease, GSD types I and III, and Niemann-Pick disease. Systematic biochemical evaluation was essential in reaching the correct dual diagnosis.

The biochemical significance of this rare association lies in:

1. Enzymatic Pathway Intersection: Both disorders involve specific enzyme deficiencies affecting distinct but essential biochemical pathways
2. Diagnostic Challenge: Routine tests may miss Factor XIII deficiency, highlighting the importance of specific enzyme activity assays
3. Genetic Implications: Consanguinity increased the risk for these autosomal recessive conditions
4. Management Complexity: Treatment must address both the glycogen metabolism disorder and coagulation defect

CONCLUSION

This case demonstrates how thorough biochemical evaluation can unravel complex clinical presentations involving multiple metabolic pathways. The coexistence of GSD III and Factor XIII deficiency represents a rare association with important implications for diagnosis, management, and genetic counselling. Understanding the biochemical basis of both disorders was crucial for accurate diagnosis and appropriate management of this unique case.

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