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CASE REPORT

A Rare Cause of Prolonged Prothrombin Time: Alagille Syndrome

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Abstract

Alagille syndrome (ALGS) is a rare genetic disorder characterized by bile duct aplasia accompanied by cholestatic liver disease and multisystem involvement, including typical facial features, congenital heart anomalies, butterfly vertebrae, ophthalmologic abnormalities, and renal anomalies. It is associated with mutations in cell signaling pathway genes such as JAG1 (Jagged Canonical Notch Ligand 1) and NOTCH2 (Notch Receptor 2)1 . Its reported incidence ranges from 1 in 70,000 to 1 in 100,000; however, with the development of molecular screening tests, the true prevalence is estimated to be approximately 1 in 30,0002. Due to the absence of bile ducts, bile flow to the intestine is impaired in ALGS, which may lead to vitamin K deficiency, prolonged INR, and bleeding manifestations. In this study, we present a patient with Alagille syndrome who developed severe coagulopathy and bleeding manifestations due to vitamin K deficiency associated with cholestasis. Clinical findings, laboratory results, imaging studies, and treatment response were evaluated. Alagille syndrome may present with vitamin K deficiency–related coagulopathy and bleeding due to impaired bile flow and fat-soluble vitamin malabsorption. Therefore, monitoring coagulation parameters and early recognition of vitamin deficiencies are important for preventing bleeding complications in patients with ALGS.

Keywords: *Alagille syndrome, Coagulopathy, Vitamin K deficiency*

Ciddi Koagulopati Nedeni Alagille Sendromu

Özet

Alagille sendromu (ALGS), safra yolu aplazisi ile karakterize, kolestatik karaciğer hastalığı ve tipik yüz görünümü, konjenital kalp anomalileri, kelebek vertebra, oftalmolojik anormallikler ve renal anomaliler gibi multisistem tutulumun eşlik ettiği nadir bir genetik hastalıktır. JAG1 (Jagged Canonical Notch Ligand 1) ve NOTCH2 (Notch Receptor 2) gibi hücre sinyal yolak genlerindeki mutasyonlarla ilişkilidir[1]. Bildirilen insidansı 70.000'de 1 ile 100.000'de 1 arasında değişmektedir; ancak moleküler tarama testlerinin gelişmesiyle birlikte gerçek prevalansın yaklaşık 30.000'de 1 olduğu tahmin edilmektedir[2]. ALGS'de safra yollarının yokluğu nedeniyle safranın barsağa akışı

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bozulur; bu durum vitamin K eksikliğine, INR uzamasına ve kanama bulgularına yol açabilir. Bu çalışmada, kolestaza bağlı vitamin K eksikliği sonucu ciddi koagülopati ve kanama bulguları gelişen Alagille sendromlu bir hasta sunulmuştur. Klinik bulgular, laboratuvar sonuçları, görüntüleme incelemeleri ve tedavi yanıtı değerlendirilmiştir. Alagille sendromu, safra akımının bozulmasına ve yağda çözünen vitaminlerin malabsorpsiyonuna bağlı olarak vitamin K eksikliği ile ilişkili koagülopati ve kanama ile prezente olabilir. Bu nedenle, ALGS hastalarında koagülasyon parametrelerinin izlenmesi ve vitamin eksikliklerinin erken tanınması, kanama komplikasyonlarının önlenmesi açısından önemlidir.

Anahtar Kelimeler: *Alagille sendromu, koagulopati, vitamin K eksikliği*

Case:

A 24-year-old male patient had complaints of frequent lung infections and had been followed with diagnoses of growth retardation and asthma since the age of 7. Verruform lesions developed on the patient's skin, and he had been receiving regular IVIG replacement therapy with a diagnosis of immunodeficiency. The patient was icteric and described intermittent bloody stools. Endoscopic examination performed for this reason revealed a duodenal appearance compatible with celiac disease. Duodenal biopsy was reported as celiac disease.

Magnetic resonance imaging performed due to elevated liver enzymes showed that the liver was enlarged to 176 mm in the midclavicular line and the spleen measured 159 mm. The intrahepatic bile ducts were mildly focally dilated in some areas on both the right and left sides, more prominent on the left. The common bile duct and proximal choledochus measured 6 mm, which was considered mildly dilated. Liver biopsy showed marked reduction in bile duct numbers (ductopenia) and moderate lymphocytic infiltration. Based on all these findings, Alagille syndrome was suspected in the patient.

With suspicion of ALGS, NOTCH1 mutation analysis was performed, but it was found to be negative.

The patient received an intramuscular NSAID injection due to headache, and subsequently a hematoma measuring 2.5×3.0 cm extending from the left psoas muscle to the inguinal region developed. Because of the patient's elevated PT-INR and complaints of gastrointestinal bleeding, he was consulted to hematology.

Laboratory findings were as follows:

WBC: 3.2 10e3/uL, Hgb: 8.8 g/dl, Plt: 216 10e3/uL, INR: 8.6, PT: 91 s, APTT: 76.2 s, Total bilirubin: 19.8 mg/dl, Direct bilirubin: 10.9 mg/dl, Creatinine: 0.26 gr/dl, Urea: 35, AST: 135 u/l, ALT: 195 u/l, GGT: 24 u/l, ALP: 249 u/l, LDH: 259 U/l, Sedimentation: 62 mm/hour.

In the cardiological evaluation, echocardiography (ECHO) showed that all cardiac chambers were of normal size and wall thickness was normal. Cardiac wall movements were normal, valve

structures and flows were normal, and the interventricular septum (IVS) and interatrial septum (IAS) were normal. The ejection fraction (EF) was 60%.

Because coagulation tests were prolonged, coagulation factor levels were measured, and Factor II, IX, X, and XI were found to be low. Fresh frozen plasma (FFP) and vitamin K replacement were administered. After replacement therapy, the patient's INR returned to normal levels and bleeding findings resolved. The bleeding and prolonged INR were considered to be due to vitamin K deficiency secondary to Alagille syndrome, and regular vitamin K replacement was recommended for the patient.

Discussion and Conclusion

Alagille syndrome is a rare syndrome accompanied by multiple system anomalies. It is usually diagnosed during childhood. Alagille syndrome (ALGS) is a multisystem autosomal dominant disease characterized by intrahepatic bile duct paucity and cholestasis with variable expression. It is most commonly associated with JAG1, and less frequently with NOTCH2 pathogenic variants[1] .Diagnosis is generally made by evaluating clinical and histopathological findings together. Essentially, the combination of bile duct paucity and accompanying major clinical features is guiding in the diagnosis[1]. The incidence is approximately 1/70,000–1/100,000, but with the widespread use of molecular diagnostic methods, the true prevalence may be higher (approximately 1/30,000)[2,3].

The clinical presentation of ALGS may range from infancy to adulthood; some patients may be diagnosed in adulthood with atypical findings[4,5] .Publications focusing on the management of adult ALGS emphasize that cholestasis-related complications, nutritional problems, and fat-soluble vitamin deficiencies are clinically critical in adult patients[4]. In our case, growth retardation and recurrent infections since childhood, followed by prominent cholestasis and bleeding findings in adulthood, support the variable phenotype of the disease.

The marked reduction in bile duct numbers detected in liver biopsy is typical for ALGS; however, "paucity of bile ducts/ductopenia" can also be seen in other cholestatic diseases, therefore differential diagnosis should be evaluated together with clinical and genetic data[6,7] . In this context, although histopathology in our case was compatible with ALGS, the phenotype not being completely classical—for example the absence of cardiac findings—was considered consistent with the known variable expression of ALGS[1,4,5].

The most striking aspect of this case was the presence of severe coagulopathy (INR 8.6, prolonged PT/aPTT) and the development of a significant hematoma after minor trauma and

intramuscular analgesic injection, together with a history of gastrointestinal bleeding. In cholestasis, decreased bile flow impairs fat absorption and may lead to deficiencies of vitamins A, D, E and especially vitamin K. Vitamin K deficiency leads to decreased levels of vitamin K-dependent factors (II, VII, IX, X; and also protein C/S), resulting in prolonged PT/INR and bleeding diathesis[8] . In cholestatic liver diseases, vitamin K deficiency may present with clinical bleeding, and oral prophylaxis may sometimes be insufficient, requiring parenteral replacement[8]. In our case, detection of decreased levels of Factor II, IX, and X (and also XI) and the rapid normalization of INR after FFP and vitamin K replacement strongly support that the main mechanism of bleeding was vitamin K deficiency secondary to cholestasis.

In ALGS, gastrointestinal bleeding may be the first presenting symptom in some cases. In a case report reported in childhood, gastrointestinal bleeding was described as the first manifestation of ALGS, and coagulation tests improved with vitamin K replacement[9]. In this respect, our case demonstrates that the same pathophysiological mechanism may lead to severe coagulopathy in adulthood, and that rapid replacement response has both diagnostic and therapeutic value.

From a genetic perspective, correct selection of target genes is important in cases suspected of ALGS. The main genes of the disease are JAG1 and NOTCH2 (1,2). In our case, NOTCH1 analysis was performed and found to be normal. This situation shows that if the appropriate gene panel is not selected despite high clinical suspicion, the contribution of genetic evaluation to diagnosis may remain limited. Therefore, confirmation with an appropriate panel including JAG1 + NOTCH2 is recommended in patients whose clinical and biopsy findings are suggestive of ALGS[1,2] .

The presence of immunodeficiency requiring IVIG replacement, verruform lesions, and recurrent infections in the case is also noteworthy. It has been shown in experimental/immunological studies that the Notch/Jagged pathway plays an important role in T-cell responses and immune regulation, and that Jagged1-related interactions may play a critical role in human T-cell immunity[10]. In addition, there are clinical reports suggesting immune dysregulation in ALGS[11]. However, in this case it is not clear whether the immunodeficiency is part of the ALGS phenotype or an independent comorbidity. Therefore, multisystem follow-up is important in such patients[4,11].

Although cardiac anomalies are an important component of ALGS, they may not be present in every case, and the expression of the disease is highly variable[1,4,5]. In our case, the normal ECHO findings support the variable phenotype of ALGS.

In conclusion, this case shows that vitamin K deficiency secondary to cholestasis may lead to severe coagulopathy and clinically significant bleeding in adult patients diagnosed with ALGS.

Therefore, regular coagulation monitoring, proactive evaluation of fat-soluble vitamin deficiencies, and parenteral replacement when necessary may be critical in preventing bleeding complications in patients with ALGS[4,8] .

References

1. **Spinner NB, Loomes KM, Krantz ID, Gilbert MA.** Alagille syndrome. In: GeneReviews® [Internet]. Seattle (WA): University of Washington; 2024 [cited 2026 Mar 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1273/
2. **Diaz-Frias J, Kondamudi NP**. Alagille syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2026 Mar 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507827/
3. **Reynal F, Camoin A, Tardieu C, Fabre A, Blanchet I.** Oral findings in children with congenital cholestatic disease: a systematic review of case reports and case series. *Archives de Pédiatrie*. 2023;30(6):427–437.
4. **Ayoub MD, Bakhsh AA, Vandriel SM, Keitel V, Kamath BM**. Management of adults with Alagille syndrome. *Hepatology International*. 2023;17(5):1098–1112.
5. **Saleh M, Kamath BM, Chitayat D**. Alagille syndrome: clinical perspectives. *Applied Clinical Genetics*. 2016;9:75–82.
6. **Gilbert MA, Loomes KM.** Alagille syndrome and non-syndromic paucity of the intrahepatic bile ducts. *Translational Gastroenterology and Hepatology*. 2021;6:22.
7. **Figiel SC, Franco A, Pucar D, Lewis KN, Lee JR**. Paucity of biliary ducts: a rare etiology of neonatal cholestasis. *Journal of Radiology Case Reports*. 2012;6(2):29–35.
8. **Sakwit A, Pongphitcha P, Komvilaisak P, Ochiai M, Takahashi D, Suga S**, **et al.** Vitamin K deficiency bleeding in children with cholestatic liver disease: a systematic review and meta-analysis. *Research and Practice in Thrombosis and Haemostasis*. 2025;9(3):102847.
9. **Campos TP, Baldanza PSG, Brandão MAB**. Gastrointestinal bleeding as the first manifestation of Alagille syndrome: a case report. *Residência Pediátrica*. 2024;14(1).
10. **Le Friec G, Sheppard D, Whiteman P, Karsten CM, Shamoun SAT, Laing A, et al**. The CD46-Jagged1 interaction is critical for human TH1 immunity. *Nature Immunology*. 2012;13(12):1213–1221.
11. **Shamoun ST, Le Friec G, Spinner N, Kemper C, Baker AJ**. Immune dysregulation in Alagille syndrome: a new feature of the evolving phenotype. *Clinical Research in Hepatology and Gastroenterology*. 2015;39(5):566–569.