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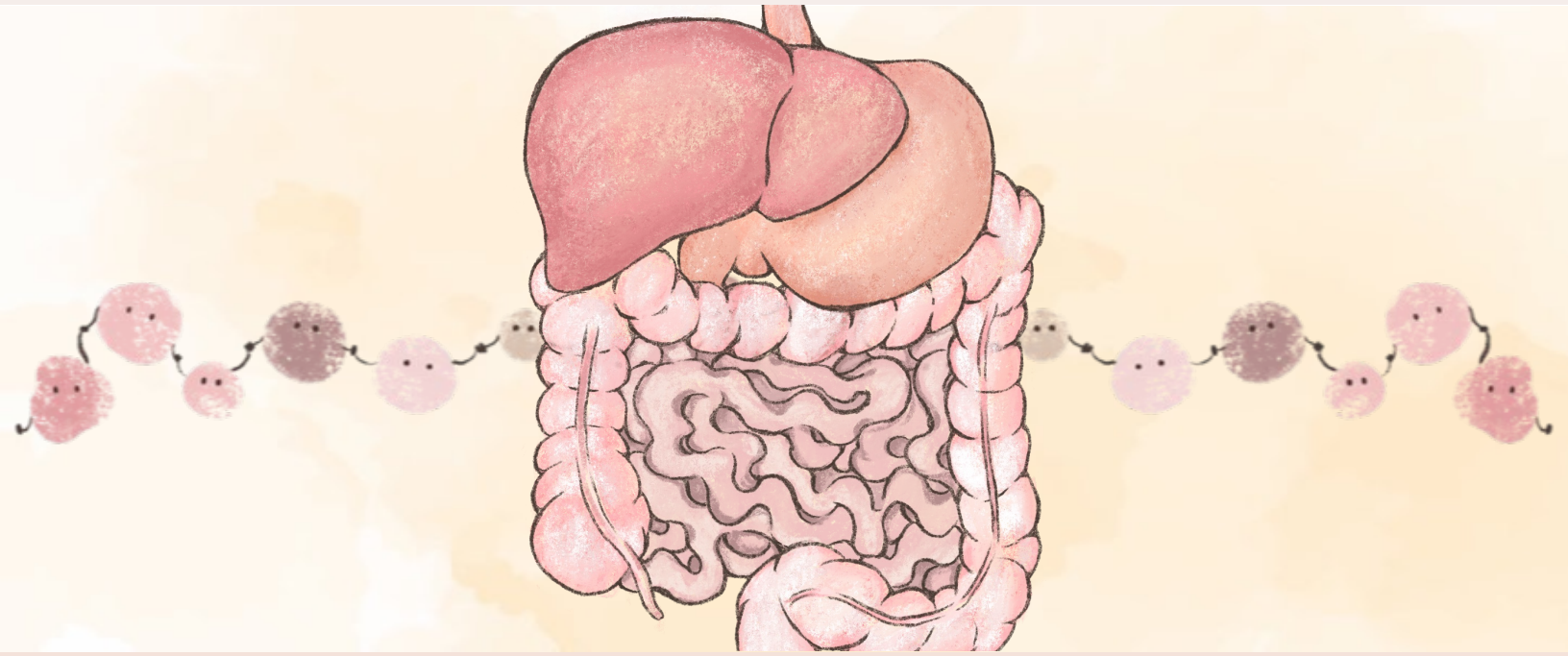

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Original Article

Liver Injury in Children with COVID-19: A Systematic Review

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Abstract:

Background: The rapid global spread of coronavirus disease 2019 (COVID-19) infection has become a major health issue with high morbidity and mortality rates. COVID-19 in children showed different unique presentations. Besides respiratory symptoms, a growing body of evidence indicates multi-organ manifestation, including liver involvement. In this regard, several data supported an association between COVID-19 infection and liver injury in adults, while on the other hand, there is compelling but currently limited evidence in children. In this systematic review, we summarize data of updated literature regarding the evidence of acute liver injury in children with COVID-19.

Methods: Online scientific articles were explored on PubMed and Google Scholar databases using keywords. The systematic review was performed under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Results: The literature search yielded 238 articles, of which 16 were identified as relevant to the topic and met the inclusion criteria. A total of 564 pediatric patients were confirmed positive for COVID-19 by PCR examination, involving 298 (52.9%) boys and 266 (47.1%) girls with an age range of 1 day - 17 years. Liver injuries have been reported in pediatric COVID-19 patients, with prevalence ranging from 1.5 to 52%.

Conclusion: SARS-CoV-2 virus infection in children shows a unique presentation. Several reports suggest that liver injury correlates with the severity of COVID-19 disease. Therefore, monitoring liver function in COVID-19 patients is important to assess the prognosis.

Keywords: acute liver injury, children, COVID-19, prognosis

Introduction

COVID-19 is a disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The prevalence of COVID-19 in children is substantial and with unique manifestations, which are diverse from COVID-19 cases in general adult population. COVID-19 was predominantly clinically manifested in the respiratory

tract at the beginning of the pandemic. However, recent data suggest that SARS-CoV-2 infection can cause systemic inflammation with multi-organ involvement, known as Multisystem Inflammatory Syndrome in Children (MISC). In addition, ACE2 receptor, the functional receptor for SARS-CoV-2 to enter cells, was expressed in several other organ systems, including the gastrointestinal, liver, bile ducts, kidney, cardiovascular, nervous system, and integument.[1] This explains the emergence of extrapulmonary manifestations in COVID-19.[2] Manifestations of liver involvement in pediatric COVID-19 is a relatively rare condition but often with a poor prognosis. Thus, it requires special attention.

The pathophysiology of liver injury in COVID-19 is thought to be due to virus, inflammation, hypoxic-ischemia/micro-thrombosis, and drugs.[3] Several studies have reported signs of liver injury in COVID-19 patients, including increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), increased bilirubin levels, and prolongation of prothrombin time (PT).[4,5] Case reports also show acute liver failure and fulminant hepatitis in patients with severe COVID-19. However, case reports of liver involvement in pediatric COVID-19 patients are limited and show heterogeneous results. Moreover, the correlation between liver involvement and the severity as well as prognosis of COVID-19 in children is still unclear. Therefore, this systematic review aims to determine the incidence of liver injury in pediatric patients with COVID-19 and its relationship to prognosis.

Methods

Literature Search

Online scientific articles were explored on PubMed and Google Scholar databases using keywords (MesH Term) of "SARSCoV-2," "COVID-19," "coronavirus," "children", "pediatric", "liver", " hepatitis", "liver injury", "alanine aminotransferase (ALT)", "aspartate aminotransferase (AST)", gamma-glutamyl-transpeptidase (GGTP)", "alkaline phosphatase (ALP)", "lactate dehydrogenase (LDH)", "bilirubin", "albumin", "international normalized ratio (INR)", "prothrombin time (PT)".

The inclusion criteria for research articles include publication in English; full text available; retrospective or prospective or cross-sectional observational study designs and case reports containing data on hepatic manifestations of COVID-19 in children; the age of the study subject <18 years and confirmed COVID-19. Meanwhile, the exclusion criteria were duplicate articles; only abstract available; review articles; systematic reviews; meta-analyses; comment articles; and letters to editors. The systematic review was performed under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Figure 1**).

Data Extraction

Data contained in the articles were then extracted, including lead author, year of publication, country, type of study, number of subjects, age of subjects, gender, comorbid liver disease, clinical symptoms, laboratory findings, and association with severe COVID-19 symptoms. Data extraction was performed by a minimum of two authors independently. The data was recapitulated in an excel file by each investigator and then compared. The differences found would be resolved by a third author.

Results and Discussion

The literature search yielded 238 articles, of which 16 were identified as relevant to the topic and met the inclusion criteria. A PRISMA diagram that describes in detail the systematic search strategy is shown in **Figure 1**. The articles included retrospective studies, cohorts, case series, and case reports published in 2020-2021. A total of 564 pediatric patients were confirmed positive for COVID-19 by PCR examination, involving 298 (52.9%) boys and 266 (47.1%) girls with an age range of 1 day - 17 years. Recently, liver involvement has been reported in pediatric patients with COVID-19. Clinical manifestations include nausea, vomiting, drinking intolerance, anorexia, abdominal pain, and even jaundice. Meanwhile, the most frequently reported markers of liver injury include elevated alanine transaminase (ALT), aspartate transaminase (AST), and elevated bilirubin levels. Data reporting decreased levels of albumin, prothrombin time (PT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) are limited. Although not all studies reported ultrasonographic features, several reported normal liver and bile duct features, one patient with hepatomegaly and another with hepatomegaly secondary to hepatic steatosis. Characteristics of case reports and studies on the manifestations of acute liver injury in pediatric patients with COVID-19 are shown in **Table 1**.

Manifestations of Liver Injury in Pediatric COVID-19 Patients

COVID-19 infection in children shows unique and varied clinical manifestations. A large retrospective cohort study reported that the manifestations of COVID-19 in pediatrics included 16.5% with respiratory symptoms (cough, shortness of breath), 13.9% with gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), 8.1 % with skin symptoms (rash), 4.8% with neurological manifestations (headache), and 18.8% with non-specific symptoms (fever, weakness, muscle aches, joint pain, impaired smell, and taste).[8] Although not as much as reported in adult patients, liver lacerations due to COVID-19 in pediatrics were recorded and characterized by significant abnormalities in liver enzyme levels.[9]

Dooki et al. reported an increase in ALT (27.8%) and AST (38.9%) levels of 18 pediatric COVID-19 patients in Iran.[10] Xia et al. also reported similar results, with an increase in ALT levels (>40 U/dL) in 25% of 36 pediatric patients with COVID-19.[11]

Following other studies, Perez et al. showed that of 219 pediatric patients with COVID-19, the ALT levels were increased to >40 IU/dL in 105 (36%) subjects, in which 31% (n=69) in pediatric patients with COVID-19 and 51% (n=36) in children with MIS-C. Pediatric patients with MIS-C have a 2.3 times risk of an increase in ALT compared with non-MISC pediatric COVID-19 patients.[5]

A retrospective study involving 8 cases of children with severe or critically ill COVID-19 admitted to the PICU in Wuhan (aged two months to 15 years) reported elevated ALT levels in 50% of cases with normal bilirubin levels.[12] A cohort study by Qiu et al. analyzed 36 pediatric patients (0-16 years) with confirmed COVID-19 at three separate hospitals in Zhejiang, China, found only two patients (5.5%) had elevated ALT and AST levels.[13] A retrospective study of 77 pediatric patients with COVID-19 also noted the increased level of ALT in 1 case (1.5%), AST in 7 cases (10.3%), ALP in 7 cases (28%), while total bilirubin, direct bilirubin, albumin, and INR were normal.[14] Other reports mentioned an increase in ALT and AST levels along with normal levels of bilirubin, albumin, PT, and INR in pediatric patients with COVID-19.[15] Jiehao et al. showed a relatively low prevalence of manifestations of liver injury, with 1 in 10 pediatric patients with COVID-19 (10%).[16]

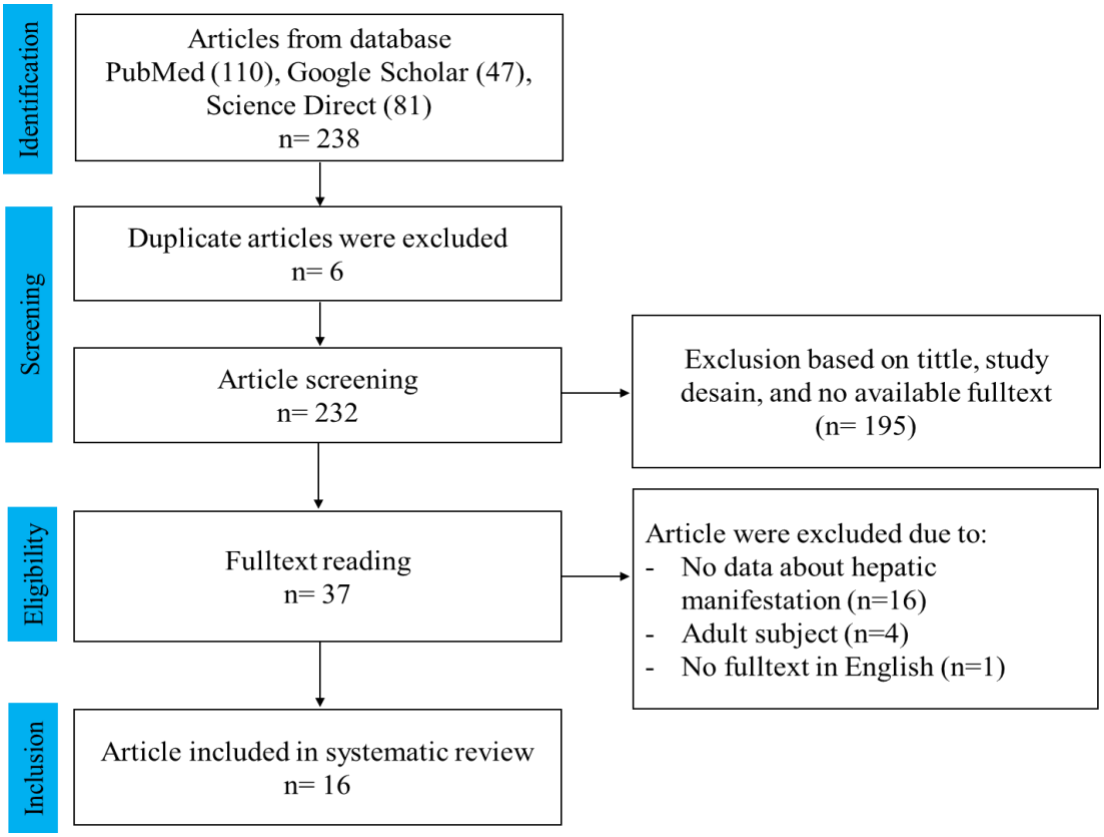

Figure 1. PRISMA diagram.

Table 1. Prevalence and manifestation of liver injury in children with COVID-19

No	Author, Year	Country	Study	Number of subjects	Gender, Age	Clinical Manifestation	Marker of liver injury	Correlation with severity	Conclusion
1	Sgouropoulou V et al. (2021)	Greece	Case Report	1	Male, 5 years old	Nausea, vomitting	AST 526 IU/L (↑) ALT 1413 IU/L (↑) ALP 277 IU/L (↑) Total bilirubin 0.4 mg/dL (N) Direct bilirubin 0.15 g/dL (N) Albumin 4.6 g/dL (N) INR 1.35 (N) PT 15.1 s (N)	Not evaluated	Increase of liver enzyme which is sign of severe acute liver injury correlated with SARS-CoV-2 infection in children
2	Cui Y et al. (2020)	Iran	Case Report	1	Male, 11 years old	Fever, jaundice, abdominal pain	AST 1038 U/L (↑) ALT 1260 U/L (↑) Albumin 3.7 g/dL (N) Gamma GT 30 U/L (N) Total bilirubin 19.2 mg/dL (↑) Direct bilirubin 16 mg/dL (↑) CRP 29 mg/L (↑) Ammonia 186 mmol/L (↑) Lactate 56 mg/dL (↑) PT 29.4 s ; INR 3.8 (↑)	Not evaluated	Fulminant hepatitis was reported in children with severe COVID-19
3	Saeed et al. (2021)	Iran	Case Report	1	Male, 11 years old	Fever, jaundice, abdominal pain	AST 2030 U/L (↑) ALT 690 U/L (↑) ALP 387 U/L (↑) Total bilirubin 35.4 (↑) Direct bilirubin 21.6 (↑) LDH 5660 (↑) PT 15.9 s ; INR 1.3 (↑)	Patient died due to fulminant hepatitis	Acute liver injury with fulminant hepatitis occurred in children with severe COVID-19
4	Sica et al. (2021)	Italy	Case Report	1	Male, 14 years old	Dehydration, jaundice, diffuse abdominal pain,	ALT 143 IU/L (↑) AST	A new onset hepatic steatosis in children with SARS-CoV-2	Non-alcoholic hepatic steatosis was reported in

						hepato-splenomegaly, palmoplantar erythema, warm extremities, weak pulse, CRT 3-4 s	Normal bilirubin serum level Abdominal ultrasonography: secondary hepatomegaly due to hepatic steatosis	infection, which is a sequelae of severe COVID-19manifestation, MIS-C	children with MIS-C
5	Perez et al. (2021)	USA	Case series	2	Male, 16 years old	Patient 1: Jaundice, abdominal pain, nausea, non-bloody and non-bilious vomiting, low intake, dark urine	Increase of serum AST (655 U/L), total bilirubin/direct bilirubin (3.6/2.2 mg/dL), gamma GT (301 U/L) Albumin 5.0 g/dL (N) INR 1.1 (N) Ultrasonography: normal liver and biliary duct	Not evaluated	Acute hepatitis with clinical jaundice and cholestasis without biliary obstruction, associated with SARS-CoV-2 infection
					Female, 17 years old	Patient 2: Fever for 4 days, acute onset of jaundice, dark urine	Increase of serum AST (154 U/L), total bilirubin/direct bilirubin (3.4/1 mg/dL), gamma GT (147 U/L). INR, albumin and platelet were within normal range. Ultrasonography: hepatomegaly (16.1 cm liver span) with normal echogenicity, without gallstone, sludging, or dilatation of the bile duct	Not evaluated	
6	Cui Y et al. (2021)	China	Case report	1	Female, 55 days old	Jaundice	Increase of AST 100U/dL, ALT 84 U/dL, total bilirubin 33.7 mg/dL, direct bilirubin 25.2 mg/dL	Not evaluated	Abnormal liver function was found in infant with COVID-19
7	Jiehao et al. (2021)	China	Case series	10	3-131 months (mean 74 months)	No available data	Median value of ALT: 18.5 U/L (N), AST: 27.7 U/L (N), one patient	No available data	10% children with COVID-19 have significant

					ratio male: female 1:1		with ALT 100 U/L (↑) and AST 142 U/L (↑)		increase of transaminase
8	Perez A et al. (2021)	USA	Retrospective study	291 patients (220 with COVID-19 and 71 with MIS-C)	2- 21 years old	No available data	Increase of ALT > 40 IU/L (mild to moderate liver injury) in 36% (n=105) of subjects; which is 31% (n=69) in children with COVID-19, and 51% (n=36) in children with MIS-C. Severe liver injury (ALT>200IU/L) was reported in 8% COVID-19 and 4% MIS-C	Patient with MIS-C increase risk of liver injury 2.3 times	Involvement
9	Dooki et al. (2020)	Iran	Retrospective study	18	Age under 18 years old	Fever, anorexia, malaise, nausea, abdominal pain	Increase of ALT in 5/18 (27.8%) patients Increase of AST in 7/18 (38.9%) patients	Patient with increase of liver enzyme was not correlated with severity of COVID-19 respiratory manifestation	Increased of liver enzyme in children with confirmed COVID-19
10	Qiu et al. (2020)	China	Cohort study	36	0-16 years old	No available data	Increase of ALT in 2 patients (mild case) and AST in 3 patients (2 mild case and 1 mild case), 6 patients (severe case)	No available data	Increase of liver enzyme in children with COVID-19
11	Sun et al. (2020)	China	Retrospective study	8	2 months-15 years old	No available data	Increase of ALT in 4 from 8 patients (50%) severe COVID-19 patient in ICU	No available data	
12	Wang et al. (2020)	China	Retrospective study	77	44 (57.1%) male and 33 (42.9%) female, median age 10 years old	No available data	Increase of ALT in 1 case (1.5%), AST in 7 cases (10.3%) ALP in 7 cases (28%) Total bilirubin, direct bilirubin, albumin, and INR were normal	No significant difference in liver function in pneumonia compared to non-pneumonia group ($p<0.05$)	Increase of liver enzyme in COVID-19 patient was not associated with pneumonia

13	Xia et al. (2020)	China	Retrospective study	20	1 day old to 14 years and 7 months old (median age 2 years old 1.5 months)	No available data	Increase of ALT (>40 U/L) in 25% patients	No available data	Increase of ALT in children with COVID-19
14	Liu et al. (2020)	China	Retrospective study	46	Infants less than 1 year old (IQR 2-7 months)	No available data	ALT (↑) in 11 patients (25%), and AST (↑) in 20 patients (45.45%). Albumin (↓) in 8 cases (18.18%). Bilirubin (↑) in 6 cases (13.64%)	Complication of liver injury in 20 (45.45%) moderate COVID-19 cases	Infants with SARS-CoV-2 infection have higher risk of liver injury compared to children and adult
15	Wang et al. (2020)	China	Retrospective study	31	6 months-17 years old	No available data	Increase of ALT AST in 22% cases	No available data	Increase of ALT and AST in children with COVID-19
16	Tan et al. (2021)	China	Retrospective study	20	7 years (1-12 years old)	No available data	Increase of AST in 10% cases	No available data	Increase of AST in children with COVID-19

s: seconds, CRT: capillary refill time, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase , PT: prothrombin time, INR: international normalized ratio, CRP: C-reactive protein, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase, MIS-C: Multisystem Inflammatory Syndrome in Children, N: normal, ↑: increase ,↓ : decrease

Interestingly, a report mentioned that two pediatric patients with COVID-19 who had elevated ALT, AST, and bilirubin levels apparently had normal liver and biliary system ultrasound results. This indicates the presence of acute hepatitis with clinical jaundice without biliary obstruction in SARS-CoV-2 infection.[5] Sica et al. demonstrated a new onset of hepatic steatosis in a 14-year-old boy patient with SARS-CoV-2 infection, which may be one of the sequelae of severe manifestations of COVID-19, known as MIS-C.[17]

Fulminant acute hepatitis was also declared in an 11-year-old patient with severe COVID-19 and complaints of fever, persistent abdominal pain, and jaundice. Laboratory parameters found the AST levels of U/dL 2030; ALT 690 U/dL; ALP 387 U/dL; total bilirubin 35.4 mg/dL; direct bilirubin 21.6 mg/dL; LDH 5660; and the elongation of PT in 15.9 seconds and INR 1.3.[7]

The acute liver laceration was found in confirmed COVID-19 infants aged 55 days, with recorded AST levels of 100 U/dL, ALT 84 U/dL, total bilirubin 33.7 mg/dL, and direct 25.2 mg/dL.[18] Moreover, Zhu et al. mentioned that 2 of 10 newborns from mothers with confirmed COVID-19 had elevated liver enzyme levels. Manifestations of liver involvement in infants are thought to be associated with the tissues' immaturity and the liver's immune system.[19]

From several case reports and studies in this systematic review, data on the prevalence of liver injury manifestations in children ranged from 1.5 to 50%. The clinical features include nausea, vomiting, decreased intake, abdominal pain, and jaundice. Meanwhile, the liver injury criteria used were increased AST and/or ALT up to 3 times the upper limit of expected values.[20] However, several other studies used the criteria for an increase in ALT of >40 U/dL and AST of >37 U/dL.[11,14] Elevated AST and ALT were more common than elevated bilirubin levels, prolonged INR, and decreased albumin levels. Data regarding radiological and histopathological features of the liver in pediatric patients with COVID-19 were limited. Post-mortem studies on COVID-19 patients with acute liver laceration showed steatosis, mild sinusoidal dilatation, and minimal lymphocytic infiltration. These features are not specific whether due to SARS-CoV-2 infection, hypoxemic conditions, or drug-induced. However, the sample contains viral inclusions in the nucleus and cytoplasm of hepatocyte cells.[21] As the growing number of reports on liver involvement in COVID-19, the American Association for the Study of Liver Diseases recommends regular monitoring of transaminases in pediatric patients with COVID-19 who have mild elevated liver enzymes.

Pathophysiology of Acute Liver Injury in Pediatric Patients with COVID-19

The mechanism underlying the increase in liver enzymes in COVID-19 patients is multifactorial due to direct viral damage, inflammatory response, hypoxic conditions, or drug cytotoxicity.[22] Some of these mechanisms can be seen in **Figure 2**.

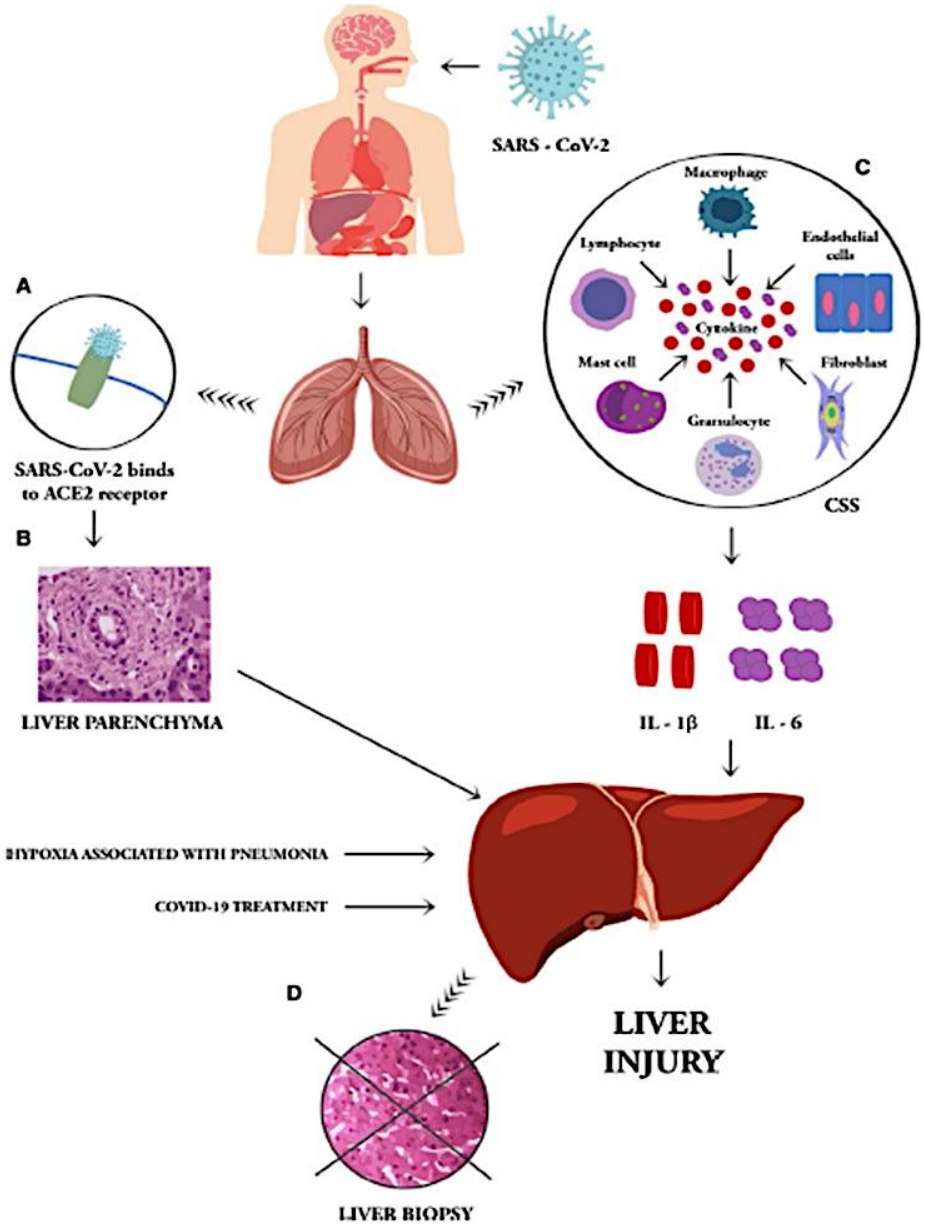

Figure 2. Pathophysiology of liver injury in COVID-19. Several mechanism underlying the increase in liver enzymes in COVID-19 including direct viral damage, inflammatory response, hypoxic conditions, or drug cytotoxicity (Adapted from de Sousa Moreira JL et al. Pathophysiology and molecular mechanisms of liver injury in

severe forms of COVID-19: an integrative review. Clinics and Research in Hepatology and Gastroenterology 2021;23:1017-22.)

Cell Damage due to Virus Infection

It is well known that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor to enter and invade host cells. Studies have reported that the ACE-2 receptor is expressed on hepatocytes, bile duct cells (cholangiocytes), and liver endothelial cells.[23] Chai et al. stated that the expression of the ACE-2 receptor was higher in bile duct cells than in type II alveolar epithelial cells. This may be due to the important role of the bile ducts in immune defense and liver regeneration. Cytopathogenic effects cause viral liver damage.[24] Wang et al. identified the appearance of hepatocytes infected with SARS-CoV-2, which showed the endoplasmic reticulum's expansion, mitochondrial edema, and decreased glycogen granules and associated with infiltration of CD4+ and CD8+ lymphocytes.[14]

Hyperinflammation

Several studies have reported an increase in serum levels of proinflammatory cytokines in COVID-19 patients with abnormal liver function. This is consistent with the histopathological picture of liver tissue that shows moderate microvascular steatosis, increased lobular and portal activity, followed by T lymphocyte overactivity.[3] The presence of SARS-CoV-2 infection in the respiratory system will induce local and systemic inflammatory reactions, by releasing proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF), that can cause a cytokine storm.[25] IL-6 is a pleiotropic cytokine that has receptors in several cells in tissues or organs of the body, including the liver. The binding of IL-6 to receptors on the hepatocyte cells will activate inflammatory signals that will attract monocytes and lymphocytes, leading to inflammatory conditions and further liver tissue damage.[26] Moreover, severe inflammatory conditions due to SAR-CoV-2 will result in an imbalance of the immune response, and the hemostasis function of the liver as a guard of immune tolerance will be disrupted. The dysregulation of the innate immune response in the liver causes the excessive production of proinflammatory cytokines by Kupffer cells, which in turn causes further inflammation.[27]

Hypoxic-Ischemic

Severe COVID-19 infection with clinical manifestations of respiratory failure can cause tissue hypoxia, including liver tissue. Hypoxic hepatitis or ischemic hepatitis can be found in severe COVID-19 patients who experience cardiac, circulatory, or respiratory complications that cause impaired liver perfusion.[28] Under conditions of systemic stress, a compensatory mechanism for decreased peripheral and splanchnic blood flow cause a decrease in blood flow to the liver, which results in hepatocellular hypoxia, especially in zone 3. Hypoxic and reperfusion injury mediated by reactive

oxygen species cause cell damage through the lipid peroxidase process. In addition, Kupffer cells can also produce proinflammatory cytokines in response to ischemia and trigger the activation and recruitment of polymorphonuclear leukocytes. This condition will cause further liver tissue damage, characterized by increased transaminases and LDH, which can improve when the hypoxic conditions are resolved.[29]

Drug-Induced Hepatotoxicity

Although several therapeutic agents are effective for COVID-19 infection, some have been reported to have hepatotoxic side effects.[30] Among these are nucleoside analog antiviral agents, such as Remdesivir, that have caused liver enzyme elevations in COVID-19 patients. Lopinavir, an antiretroviral protease inhibitor, has also been reported to cause transient elevations in serum aminotransferase levels but is often asymptomatic. Tocilizumab, an IL-6 inhibitor, often causes mild elevations in serum aminotransferase and bilirubin levels, usually transient and asymptomatic. Ivermectin, an anti-parasitic agent and used as a therapeutic regimen for COVID-19, has been reported to be associated with transient elevations of serum aminotransferases, and very few reports of ivermectin-induced liver injury have resulted in dose adjustment for patients with hepatic impairment.[31] Also, pediatric patients with COVID-19 often come with complaints of fever and are given Paracetamol. Paracetamol is said to be associated with liver damage due to its hepatotoxicity.[30]

Relationship between Liver Injury Manifestations and COVID-19 Severity and Prognosis

Reports regarding the relationship between the manifestations of liver injury with the severity and prognosis of COVID-19 infection in children are still inconclusive. Several studies have shown that COVID-19 patients with elevated liver enzyme levels do not correlate with more severe respiratory manifestations.[10,32,33] Another study also reported no significant difference in the liver function of pediatric patients with COVID-19 with and without pneumonia ($P > 0.05$).[14] However, Perez et al. noted that liver involvement in COVID-19 infection in children correlated with more severe clinical manifestations. The study also reported that pediatric patients with MIS-C had a 2.3-fold increased risk of ALT compared with those with COVID-19.[5] A meta-analysis study concluded that patients with severe COVID-19 had a higher risk of developing liver injury manifestations. Although, the incidence in pediatric patients was lower than in adults. It is thought to be due to severe COVID-19, the presence of an inflammatory process, and massive tissue hypoxia that can increase the risk of liver damage.[34]

The prognosis of COVID-19 patients with manifestations of liver injury is still indecisive. A large-scale study reported elevated AST and/or ALT correlated

significantly with mortality and intensive care hospitalization.[35] Another study also mentioned that the De Ritis ratio (serum AST and ALT) was significantly associated with mortality in COVID-19 patients.[36] However, reports in pediatric patients are still finite. Perez et al. reported that pediatric COVID-19 patients with elevated ALT had more severe clinical manifestations and longer ICU stay ($p<0.05$).[4]

Another interesting thing is that almost 10% of COVID-19 patients show manifestations only in the digestive system. Patients with early digestive system symptoms were recorded to have delayed diagnosis, so they tend to progress to severe disease, critical conditions, and poor outcomes. Therefore, increasing attention to the manifestations of the digestive system in COVID-19 infection, especially for pediatric patients, is crucial. The American Association for the Study of Liver Diseases recommends regular monitoring of transaminases in pediatric patients with COVID-19 who have mild elevations of liver enzymes. Pediatric COVID-19 patients with jaundice, elevated ALT/AST over 500 U/mL, and new-onset liver decompensation should be investigated further in the hospital. Thus, it is expected that liver laceration in pediatric patients with COVID-19 can be reduced to improve outcomes and prognosis.[34]

Conclusion

SARS-CoV-2 virus infection in children shows a unique presentation. Liver injuries have been reported in pediatric COVID-19 patients, with prevalence ranging from 1.5 to 52%. Clinical manifestations include nausea, vomiting, abdominal pain, drinking intolerance, and jaundice. Elevated levels of ALT and AST are more frequently reported as a sign of liver injury. Several pathomechanisms of acute liver injury in COVID-19 have been proposed, including direct viral infection, inflammation, hypoxia-ischemia, and drug induced. In addition, several reports suggest that liver injury correlates with the severity of COVID-19 disease. Therefore, monitoring liver function in COVID-19 patients is important to assess the prognosis.

Conflict of Interest

None declared.

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Original Article

Risk Factors Affecting the Length of Improvement of Nutritional Status in Children with Congenital Heart Disease and Malnutrition

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Abstract:

Background: To date, limited data are available regarding the factors that contribute to the delay of improvement in nutritional status as well as data regarding the optimal duration to improve malnutrition among children with congenital heart disease (CHD). Such data are important for pediatricians to fully optimize the nutritional status for those children prior to surgical procedure This study aims to identify those aforementioned factors in hope for better surgical outcome and quality of life of children with CHD.

Methods: This is a descriptive analytic study using retrospective cohort design to identify the factors that contribute to the delay of improvement in nutritional status among children with CHD. Variables such as the type of CHD, classification of CHD complexity, pulmonary hypertension, heart failure, corrective surgery, the route of nutrition access, pneumonia, diarrhea, special diets and patients undergoing routine control at the nutrition outpatient clinic were evaluated in this study.

Results: A total of 216 children with a diagnosis of CHD and weight-for-length z-score under -1 SD were included in this study. Based on multivariate analysis, there were two significant risk factors, which were the occurrence of diarrhea and consulting at nutrition outpatient clinic. The improvement in nutritional status in children with CHD who did not have diarrhea was faster than those with diarrhea (HR 1.94; 95% CI 1.10 – 3.47) (p value <0.025). Improvement in nutritional status of those children that underwent control at the nutrition outpatient clinic was faster than those who did not (HR 1.87; 95% CI 1.20 – 2.92) (p value <0.006).

Conclusion: Risk factors that significantly lengthen the duration of improvement in the nutritional status of CHD patients were the incidence of diarrhea and those who did not undergo control at the nutrition outpatient clinic.

Keywords: CHD, duration of nutritional status improvement, malnutrition, risk factor

Introduction

Congenital heart disease (CHD) is commonly associated with malnutrition in children. The incidence of growth failure among children with CHD is 64% in developed countries while higher number is observed in developing countries with varying incidence of 27% to 90.4%.[1] One study by Amelia et al in Indonesia reported that the incidence of wasting and stunting among children with CHD were 56.8% and 46.6% respectively.[2]

Children with CHD are known to have a higher basal metabolic rate with poorer calories intake, which explain the greater prevalence of malnutrition among those population.[3,4] There are other factors that may also exacerbate this condition, such as chronic hypoxia due to cyanotic CHD, pulmonary hypertension, heart failure, delayed surgery, dietary pattern as well as infections (pneumonia and diarrhea).[3,5-7] Several conditions that are associated with CHD have been linked to impaired growth in children. Acyanotic CHD is reported to be associated with underweight, pulmonary hypertension is associated with wasting and lastly, cyanotic CHD as well as single ventricle disease are associated with stunting in children.[8] Malnutrition in children with CHD is known to negatively impact the surgical outcome as well as morbidity and mortality.[4] According to a study, CHD children with good nutritional status have lower complication rates during surgical intervention later on.[9]

Devaera et al. reported that in general, there 5 risk factors that cause children with CHD to be more susceptible to malnutrition.[10] First is the increased energy requirement among those children which is due to increased basal metabolic rate, total energy expenditure as well as nutritional requirement for cardiac and respiratory muscles. Moreover, conditions such as infection and prematurity may further increase the energy requirement. Second, children with CHD are most likely to have decreased food intake due to anorexia, early satiety as well as dysphagia and gastrointestinal reflux disease. Third, increased loss of nutrients is commonly found in those children due to gastrointestinal malabsorption, hyperosmolarity, protein-losing enteropathy and loss of electrolytes from the kidney. Fourth, children with CHD are inefficient in utilizing nutrients as a result of acidosis, cellular hypoxia and increased pulmonary pressure. Lastly, other factors such as chromosome disorder, nutritional impairment during pregnancy as well as low birth weight may contribute to susceptibility of children with CHD to malnutrition.[10]

To date, limited data are available regarding the factors that contribute to the delay of improvement in nutritional status as well as data regarding the optimal duration to improve malnutrition among children with CHD. Such data are important for pediatricians to fully optimize the nutritional status for those children prior to surgical

procedure. Therefore, this study aims to identify those aforementioned factors in hope for better surgical outcome and quality of life of children with CHD.

Methods

This is a descriptive analytic study using retrospective cohort design to identify the risk factors that contribute to the delay of improvement in nutritional status among children with CHD. This study was conducted at an outpatient pediatric cardiology clinic in a national referral hospital with integrated cardiac unit. Inclusion criteria for this study were children with CHD age 0-5 years, weight-for-length z- score below -1 SD based on WHO 2005 growth chart when first admitted and were followed up until either they reached good nutritional status (z-score > - 1 SD) or at least 1 year, as well as patients who went for routine control for at least 3 times during that period at cardiology outpatient clinic. Exclusion criteria were incomplete data and patients who were lost to follow up (death or patients stopped coming for routine control). Subjects were sampled by total sampling method of those who were treated at our hospital throughout the period of 1 year (August 2016 to July 2017). The minimal number of subjects for each risk factors in this study were 38 subjects based on the formula to determine the differences between two proportion. Rule of thumb was utilized to determine the number of risk factors to be included for analysis. Dependent variable in this study was the length of time until improvement in nutritional status, while independent variables were the type of CHD, classification of CHD complexity, pulmonary hypertension, heart failure, corrective surgery, the route of nutrition access, pneumonia, diarrhea, special diets and patients undergoing routine control at the nutrition outpatient clinic.

Determination of the subject's nutritional status and stature was carried out using the WHO Anthro tool by entering the date of birth, date of monitoring, weight and height. Then the weight-for-length and height-for-age z-score data were transferred to the Statistical Package for the Social Science (SPSS) version 25 software for analysis. Factors that affect the length of time needed for nutritional improvement were assessed by using a survival analysis test for each of these factors, so that the mean or median value of the duration for nutritional improvement was obtained. Significance was evaluated using the log rank test or Breslow depending on the distribution of the data. Risk factors that had p values under 0.2 were included in the multivariate analysis. Multivariate analysis was carried out using the Cox regression test to produce a hazard ratio (HR), confidence interval, and significance. The p value <0.05 was considered significant in this multivariate test.

Results

A total of 336 children with a diagnosis of CHD and weight-for-length z-score under -1 SD were recruited in this study. However, after screening by applying inclusion and

exclusion criteria, only 216 remained eligible for this study. Baseline characteristics of all subjects are presented on **Table 1**. Children with CHD and malnutrition in this study had the same proportion of boys and girls (47% and 53% respectively). Most of our patients were under one year old with fewer number of patients were observed with increasing age groups. The median age of subjects was 9.1 months. Eighty percent of those patients presented with acyanotic CHD, while the other 20% were cyanotic. As many as 74% of CHD patients had normal birth weight (> 2500 grams), while the rest had low birth weight. The median of weight-for-length z-score during initial monitoring period was -2.73 SD. Meanwhile, by the end of follow up, the median z-score was -1.62 SD.

Table 1. Baseline characteristics of children with CHD and malnutrition.

Characteristics	Frequency
Gender, n (%)	
Boys	102 (47)
Girls	114 (53)
Age (months), median (range)	9,1 (0 – 48,7)
Age classification, n (%)	
under 1 year old	140 (65)
1-2 years old	44 (20)
2-3 years old	16 (7,4)
3-4 years old	12 (5,6)
4-5 years old	4 (1,9)
Classification of CHD, n (%)	
Acyanotic	172 (80)
Cyanotic	44 (20)
Classification of birth weight, n (%)	
<2500 gram	56 (26)
≥2500 gram	160 (74)
Weight-for-length z-score initial follow up, median (range)	-2,73 (-6,39 – -1,10)
Weight-for-length z-score end of follow up, median (range)	-1,62 (-6,56 – 1,21)
Changes in weight-for-length z-score, median (range)	1,18 (-2,85 – 6,25)

Nutritional status for each patient was collected at the first hospital admission and continued to be monitored until they had reached good nutritional status (weight-for-length z-score above 1 SD) or at least 1 year of follow up. Data regarding the nutritional status before and after follow up period are presented on **Table 2**.

Table 2. Nutritional status before and after follow up period.

Nutritional status	Initial follow up			End of follow up		
	acyanotic (n=172)	cyanotic (n=44)	p	acyanotic (n=172)	cyanotic (n=44)	p
Nutritional status						
Good nutritional status	0	0		74 (43)	10 (23)	
Mild malnutrition	38 (22)	12 (27)	0.767	38 (22)	20 (45)	0.005
Moderate malnutrition	58 (34)	14 (32)		30 (17)	10 (23)	
Severe malnutrition	76 (44)	18 (41)		30 (17)	4 (9)	
Stature						
Normal stature	102 (59)	24 (54)		110 (64)	16 (36)	
Short stature	24 (14)	10 (23)	0.490	24 (14)	16 (36)	0.002
Very short stature	46 (27)	10 (23)		38 (22)	12 (27)	

The change of nutritional status was evaluated at the end of follow up period by calculating the difference of weight-for-length z-score during that period (**Table 3**).

Table 3. Changes in nutritional status after follow up period.

Changes in nutritional status	Total 216; n (%)
Worsen	16 (7)
No changes	52 (24)
Improvement	148 (69)

The significance test was assessed by using the log rank test or Breslow test depending on the distribution of the data (**Table 4**).

Table 4. Analysis of possible risk factors that may affect the length of time needed for nutritional improvement

Risk Factors	Median of duration to improve nutritional status (months)	p-value
Classification of CHD		
Cyanotic	7.81	0.046*
Acyanotic	4.97	
Heart failure		
Yes	5.96	0.635
No	7.14	

Route of nutrition administration		
Oral	6.80	0.083*
Enteral	4.99	
Diet		
Normal/polymeric formula	7.24	0.059*
Special formula	4.99	
Pneumonia		
Yes	9.28	0.072*
No	7.23	
Diarrhea		
Yes	8.44	0.018*
No	6.54	
Routine control at nutrition clinic		
Yes	4.99	0.002*
No	8.14	

*Statistically significant (p<0.05)

There were six factors that had a p value <0.2 based on log rank test or Breslow test. Those factors were then included in multivariate analysis by using Cox regression to obtain significant risk factors with p value <0.05. There were two significant risk factors, which were the occurrence of diarrhea and consulting at nutrition outpatient clinic. The results of this multivariate analysis can be seen in **Table 5**.

Table 5. Multivariate analysis possible risk factors that may affect the length of time needed for nutritional improvement

Risk factors	Hazard ratio (95% CI)	p-value
Cyanotic CHD	1.37 (0.88 – 2.13)	0.160
Oral nutrition route	0.97 (0.64 – 1.48)	0.893
Normal diet	1.02 (0.67 – 1.55)	0.934
Pneumonia	1.64 (0.96 – 2.80)	0.069
Diarrhea	1.94 (1.10 – 3.47)	0.025*
No routine control at nutrition clinic	1.87 (1.20 – 2.92)	0.006*

*Statistically significant (p<0.05)

The improvement in nutritional status in children with CHD who did not have diarrhea was faster than those with diarrhea. Those children without diarrhea experienced an improvement in their nutritional status in 6.54 months, while those

with diarrhea experienced an improvement in 8.44 months. Multivariate analysis showed that children with CHD without diarrhea would have their nutrition improved 1.94 times faster to increase the weight-for-length z-score by 0.67 SD based on the WHO growth chart compared to the those who had experienced diarrhea.

Improvement in nutritional status of children with CHD that underwent control at the nutrition outpatient clinic was faster than those who did not. CHD patients who went for control experienced an improvement in nutritional status in a median of 4.99 months, while those who did not go for control experienced an improvement in a median of 8.14 months. Multivariate analysis showed that the CHD group that controlled the nutrition outpatient clinic experienced improved nutrition 1.87 times faster to increase the z-score by 0.67 SD based on the WHO curve compared to the CHD group that had never been in control.

Discussion

We found 2 factors that significantly contribute to delayed nutritional improvement in children with CHD; those are any episode of diarrhea and low adherence to control to pediatric nutrition clinic. Diarrhea is one of the main causes of increasing morbidity and mortality in developing countries with an estimated death in children reaching 1.5 million per year due to this disease. Complication due to frequent diarrhea, such as malnutrition, may occur through anorexia, decreased ability of food absorption, damage to the gut mucosa and loss of nutrients. Eventually, this condition may hinder the normal growth of those children. Severe diarrhea is more common in malnourished patients compared to those without. Meanwhile, malnourished children are more likely to contract infections, particularly gastrointestinal infection. Hence, both diarrhea and malnutrition may have influenced one another.[11] Our study demonstrated that diarrhea was a significant risk factor in determining the duration of improvement of malnutrition in children with CHD. Those patients with diarrhea took 8.44 months to improve their nutritional status while those without diarrhea only took 6.54 months (HR 1.97; 95% CI 1.10-3.55). Children with CHD without diarrhea were 2 times faster to see an increase of the Z-score by 0.67 SD ($p<0.023$) in comparison to those with diarrhea. However, the operational definition of the incidence of diarrhea in this study was based on medical records and history taking from parents or caregivers, not from the objective assessment during hospital admission. Therefore, it is important to note that information bias may occur.

The gut microbiota plays an important role in nutritional status as those beneficial bacteria provides both protective and metabolic function for the gastrointestinal tract. The role of microbiota on nutritional status occurs in several ways: (1) providing nutrients for colonic epithelium by producing short chain fatty acids (SCFA) which is a byproduct of polysaccharides fermentation by those bacteria, (2) induction of genes

activation which is crucial for nutrient absorption and development intestinal immune system, and (3) triggering neurotransmitter and hormone responses that affect the speed of glucose and fat metabolism, appetite, and intestinal transit time.[12] In children with CHD, especially those with cyanotic, the presence of mesenteric hypoperfusion and chronic hypoxia can disrupt the development of the gut microbiota resulting in dysbiosis.[13] On the other hand, research in Bangladesh showed that the microbiota maturation index in children with diarrhea was lower than those in normal children. This indicated that some degree of dysbiosis was occurring on children with diarrhea.[14] The presence of diarrhea on children with CHD may further disturb the already abnormal gut microbiota and hence may prolong the duration for improvement in nutritional status among those children.[12] Infections such as acute diarrhea can also trigger an inflammatory cascade resulting in decreased appetite and reduced fat mass. Research by Kosek et al., found that children who suffered from diarrhea 3-5 times a year was at risk of short stature.[15] Research in Malawi found that most patients with severe malnutrition had some coexisting infections, even if they were mild, including diarrhea.[16] Giving antibiotics in this study had been shown to accelerate healing and reduced mortality, but unfortunately it was not proven whether antibiotics can improve dysbiosis. In this study, dysbiosis was not examined because the incidence of diarrhea was only obtained based on the history taking.

Another risk factor that was also significant in determining the duration of improvement in nutritional status among children with CHD was whether or not those patients went for routine control at the nutrition outpatient clinic. There was a difference in the duration of improvement in nutritional status between CHD patients who underwent control at the nutrition outpatient clinic and those who did not. Those patients who were under control at the nutrition outpatient clinic experienced an improvement in nutritional status in a median of 4.99 months, while those who were not, experienced an improvement in nutritional status in a median of 8.14 months (HR 1.87; 95% CI 1 .20-2.92). The proportion of CHD patients with improved nutritional status was greater in those who underwent routine control compared to those who did not, indicating that regular monitoring of growth parameters is important in the nutritional management of those patients. Accurate and periodic measurements accompanied by special attention to nutritional intake and tolerance have a major impact in the management of malnutrition in children with CHD.[17] Those children who consult at the nutrition outpatient clinic will receive nutritional care in the form of an initial assessment, determination of caloric requirements, selection of diet, determination of nutritional pathways, and monitoring in the form of acceptability, tolerance and efficacy.

One study suggested that monitoring of growth should be carried out periodically through consultation with a nutritionist. Nutritional interventions such as the type of

diet, route of administration, and eating rules should be tailored individually to each patient.[18] Furthermore, regular visits to nutritionist may provide information and solve food intake problems for patients. This is also said to help parents reduce stress due to confusion in dealing with eating problems in their children.[19]

Children with CHD often suffered from hypermetabolic state in which they have an increase of 30% of resting energy expenditure and consequently exposing them to catabolic stress.[20] Furthermore, in developing countries such as Indonesia, the prevalence of malnutrition, growth failure as well as pulmonary hypertensin in children with CHD are higher due to limited access to timely surgical intervention for those children. As such, those children are left in those hypermetabolic and catabolic conditions for such a prolonged time and eventually develop malnutrition and growth failure.[21] Moreover, malnutrition that occur during preoperative in children with CHD has been associated with negative outcomes after surgery such as death, cardiac arrest, infection, increased ICU and hospital length of stay as well as longer duration of ventilation support.[22] Based on a systematic review, human breast milk is believed to be the first choice of nutrition as it is better tolerated, promotes intake and growth, and is associated with less postoperative complications for newborns who suffer from CHD.[21,23] However, in certain condition, infant formulas with a higher calorie (above 0.67 kcal/mL) can be given as an option when required. Early initiation of enteral nutrition during perioperative phase has been reported to produce better outcomes such as improve wound healing, less gastrointestinal dysfunction and reduce muscle loss. Perioperative enteral nutrition is recommended to be high in calorie and should be adjusted to individual needs or water restriction, if required. In the immediate postoperative period (0–3 days), nutrition required is approximately 35–65 kcals/kg/d since resting energy expenditure in this condition is considerably reduced.[24]

This research has several limitations. First, the interval period of control schedule at the clinic for each subject differs, hence, there was a possibility of inaccurate data regarding the exact timing of nutritional improvement in patients. Second, this was a retrospective study, so there was a possibility of both information bias and observation bias during data collection. Furthermore, medical records were not written by one person, thereby, the assessment by each physician may not the same in assessing risk factors. Retrospective study design also resulted in some subjects not being able to be assessed due to incomplete data and consequently had to be excluded. Third, in this study, monitoring time was only limited to one year, so long-term effects could not be evaluated. Lastly, in this study, we utilized weight-for-length z score to determine the nutritional status of children with CHD. However, such parameters that only depend on weight and height should be used with caution for determining the nutritional status among those children because it could mask undernutrition and may not reflect the real weight of the child. Children with CHD may present with edema and fluid

retention which may be reflected on their weight. Even though there is no gold standard to assess the nutrition status in disease-related malnutrition, Devaera et al. recommended the use of arm anthropometric assessment (triceps skinfold thickness and mid-upper arm circumference) to better evaluate the nutritional status of those children in order for appropriate monitoring and management as well as to establish correct diagnosis of the child's nutritional status, particularly in developing countries such as Indonesia.[10] Furthermore, this study also suggested that the frequency and interval of nutritional status monitoring in children with chronic illnesses, such as CHD, should be tailored according to the conditions of the each child as nutritional status is greatly influenced by the course of their illness which may change during the course of their illness and treatment.[10]

Conclusion

Based on the results of this study, most of our patients with CHD had an improvement in nutritional status (69%), while 24% had not changed and 7% had worse nutritional status after follow up period. Risk factors that significantly lengthen the duration of improvement in the nutritional status of CHD patients were the incidence of diarrhea and those who did not undergo control at the nutrition outpatient clinic. CHD patients who experienced diarrhea took almost twice as long to improve in nutritional status than those who did not experience diarrhea. On the other hand, CHD patients who underwent control at the nutrition outpatient clinic were twice as fast to improve in nutritional status than those who did not.

Conflict of Interest

None declared.

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Pediatric Hepatitis A: A Case Report

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Abstract:

Background: Hepatitis A is a systemic infection which predominantly inflame the liver due to Hepatitis-A-Virus (HAV) infection. Developing countries have higher prevalence of this disease because of poor sanitation and environment. The transmission of HAV is fecal-oral via contaminated foods or beverages.

Case: A 14-year-old boy visited emergency department with yellowish skin on body, nausea, fever, and liver enlargement. He had a bad habit of consuming unhealthy street-foods. Hepatitis A was diagnosed after history taking, physical examination and laboratory testing. Serology test was performed with positive Anti HAV IgM to confirm the disease. Liver enzymes, and bilirubin level were also increased in this patient.

Discussion: The transmission of HAV is through fecal-oral via contaminated foods or beverages. This disease can be prevented by having good personal hygiene, avoiding contaminated food, with good access to clean water and environmental sanitation. Habit of consuming street foods is a risk factor of developing HAV infection. The clinical manifestation of HAV infection includes jaundice, nausea, decreased appetite, and vomiting.

Conclusion: Diagnosis of hepatitis A requires careful history taking, physical examination and laboratory evaluation. Hepatitis A is a self-limiting disease and currently there is no specific treatment to cure this disease. Supportive treatment, hepato-protector and vitamin supplementation will improve the condition.

Keywords: children, hepatitis A, jaundice

Introduction

Hepatitis A is a systemic infection which predominantly inflame the liver due to Hepatitis-A Virus (HAV) infection. HAV infection occur globally with higher prevalence in developing countries which are associated with poor environmental condition.[1] Data from World Health Organization (WHO) in 2011 showed that Indonesia is one of the countries with high hepatitis A prevalence. In Aceh Province, subdistrict with the highest prevalence of hepatitis A is North Aceh (3,6%) compared to whole Aceh Province itself (1,4%).[2]

HAV is transmitted via fecal-oral transmission which means that people can get infected when consuming fecal-contaminated food or beverages. The clinical manifestations arise abruptly according to the phases of the infection, which are prodromal phase, icteric and convalescence. However, in some cases, HAV infection proven which is proven by serology test can be asymptomatic or with minimal symptoms without jaundice which is known as anicteric hepatitis A. The tendency of developing this condition is higher in children.[3] In this study, we aimed to present a case about pediatric hepatitis A on a 14-year-old boy.

Case

A 14-year-old boy was presented to emergency department in Zainoel Abidin General Hospital with the chief complaint of yellowish skin on face, body and extremities that occurred in the past 3 days before admission. The jaundice was progressive until one day before admission. There was history of intermittent fever in the last two days which improved after consuming antipyretic. He also complained of fatigue, intermittent right hypochondriac abdominal pain, decreased appetite, nausea, and also 2-3 times vomiting per day with around 100 cc volume each time. His urine was dark yellow with normal color of feces. He was a student in a boarding school and one of his friends had similar complaint. He also consumed lots of unhealthy street-foods.

Upon evaluation, patient was compos mentis with normal vital sign. The anthropometry measurement showed that he suffered from malnutrition (current body weight/ideal body weight 72.3%). Jaundice was present throughout the body including the sclera. Abdominal examination also showed that jaundice was also present on the abdomen without any distention. There was a right hypochondriac abdominal pain and the liver is palpated 2 cm below the costal arc. Laboratory tests showed that hemoglobin 10.8 g/dL, hematocrits 33%, leucocytes 6.2 x 10^3 cells/mm^3, SGOT (AST) 129 U/I, SGPT (ALT) 110 U/I, total bilirubin 6.96 mg/dL, direct bilirubin 4.98 mg/dL, and indirect bilirubin 1.98 mg/dL. Immuno-serology test also revealed reactive Anti-HAV IgM which confirmed the disease.

Patient was treated supportively including bed rest, diet with soft consistency, domperidone every 8 hours, curcuma every 24 hours, Vitamin E 200 IU every 24 hours, Vitamin K 10 mg every 24 hours, multivitamin supplement, and Vitamin D every 24 hours. After receiving treatments, all symptoms including jaundice progressively improved.

Discussion

Hepatitis A is a systemic infection which predominantly affect the liver because of HAV infection. A majority of HAV infection occurred in early life without symptoms and jaundice. The transmission of this disease is through fecal-oral via contaminated foods or beverages. This disease can be prevented by practicing good personal hygiene, avoiding contaminated food, as also good access to clean water and better environmental sanitation. Habit of consuming street foods is a known risk factor of developing HAV infection.[3]

The clinical manifestation of HAV infection includes systemic jaundice, nausea, decreased appetite, and vomiting approximately 2-3 times per day. Based on the pathophysiology, HAV enters human's gastrointestinal tract to the vena porta and later invades liver parenchymal tissue. Virus replicates in the hepatic cells causing damage to the parenchymal tissue. Then, virus will continuously migrate and invade another liver parenchymal cells or enter the biliary duct to be excreted through feces. Damaged liver parenchymal cells will stimulate inflammation reaction characterized by macrophage aggregation as well as Kupffer cell enlargement which may obstruct the flow of conjugated bilirubin and also reduce bilirubin excretion to the intestine. This condition will lead to the imbalance of bilirubin production and excretion from the liver which consequently causes conjugated bilirubin to be accumulated inside the liver and reflux to the intravascular. This pathophysiology is manifested as jaundice on the skin especially the sclera as well as itchiness due to deposit of bile salts on the skin tissue. Lack of conjugated bilirubin in the intestinal tract causes reduced bile acids which leads to fat metabolism disorder. Prolonged fat storage in the stomach stimulates sympathetic and parasympathetic nerve to activate the medulla oblongata and triggers the sensation of nausea, vomiting and decreased appetite.[4] The damage of liver cells during viral replication process will cause high liver enzyme concentration which can be measured as increased level of SGOT (AST) and SGPT (ALT).

In this case, liver is palpated approximately 2 cm below the costal arc. Hepatomegaly is caused by replication of HAV inside the hepatocyte. Immune system will be activated to produce specific reaction to fight and eradicate those infectious agents. Consequently, liver will be inflamed and enlarged.[5] There is no specific treatment for hepatitis A as this is a self-limiting disease. Bed rest is highly suggested combined with other supportive treatments. Intravenous treatment may be required in case of

persistent vomiting in children. Patients have to avoid alcoholic and hepatotoxic drug consumption.

Rhizoma curcuma tablet is beneficial as additional supplement in improving liver function as well as restoring appetite. Hartono mentioned that the use of 5-10 mg/kg/day dosage is proven to give hepatoprotection and repair damaged liver cells. This supplement is available in tablet-shaped containing 200 mg of curcuma. The use of hepato-protector will only reduce the symptoms and not cure the disease.[6] Vitamin combined with high protein and high calories food have to be given for patients suffering from malnutrition. Specific diet and vitamin are aimed to achieve and maintain optimal nutrition without increasing liver load.[7]

Conclusion

Hepatitis A is a systemic infection which predominantly inflame the liver due to Hepatitis-A-Virus (HAV) infection. The diagnosis is made after careful history taking, physical examination and laboratory evaluation. In this study, we presented a case of 14-year-old boy who visited the emergency department with yellowish skin on body, nausea, fever, and liver enlargement. He had a bad habit, consuming unhealthy street-foods. Hepatitis A was diagnosed after examination. The clinical manifestation of this disease depends on which phases the patient is currently in. Serology test was performed to detect the presence of Anti HAV IgM to confirm the disease. Laboratory test with high ALT/AST and bilirubin indicated the presence of damage of liver cells. Hepatitis A is a self-limiting disease, hence, there is no specific treatment to cure this disease. Supportive treatment, consuming hepato-protector and vitamin supplementation will improve the condition.

Conflict of Interest

None declared.

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Case Report

Duodenal Stenosis: A Case Report

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Abstract:

Background: Congenital duodenal stenosis in pediatric patients was often underreported due to its non-conspicuous signs and symptoms. Diagnosing duodenal stenosis is often challenging as this disease causes partial intestinal obstruction and thus presents with more indolent and atypical clinical manifestations. This case report aims to describe the atypical case of pediatric duodenal stenosis which presented with recurrent vomiting and poor weight gain as well as highlight some of the diagnostic challenges.

Case: A 7-month-old girl was admitted to the emergency room with chief complaint of recurrent vomiting in the last 2 days prior to hospital admission. Patient had a history of recurrent bilious vomiting at the age of 3 days old with a frequency of 3-4 times a day and were admitted to the hospital for 2 weeks. Parents also reported of poor weight gain in the last 3 months. Abdominal X-Ray series showed dilatation of the small intestines immediately after pylorus and stack of coins sign. Esophageal endoscopic evaluation showed signs of severe GERD with a pyloric gap as well as a suspicion of a duodenal web

Discussion: Congenital obstruction at the duodenum may occurs due to intrinsic or extrinsic etiology. Failure of duodenal re-canalization during the 8-10th week of embryological development is thought to be the main cause of intrinsic duodenal obstruction (atresia, stenosis or duodenal web). The appearance of clinical manifestation of duodenal stenosis depends on the degree of stenosis itself.

Conclusion: Congenital duodenal stenosis may present with atypical presentations in neonates which requires clinicians to be fully aware of this diagnosis to ensure timely therapy. The main management of duodenal stenosis is surgery, however fluid administration, decompressing as well as other supportive treatment are equally crucial to ensure better outcome for the patient.

Keywords: duodenal stenosis, pediatric, poor weight gain, vomiting

Introduction

Congenital duodenal stenosis in pediatric patients was often underreported due to its non-conspicuous signs and symptoms. Diagnosing duodenal stenosis is often

challenging as this disease causes partial intestinal obstruction and thus presents with more indolent and atypical clinical manifestations. Poor weight gain is one of the most common symptoms in children with duodenal stenosis. However, this clinical manifestation often undetectable by the parents due to inappropriate feeding practice or feeding the children with concentrated infant formula.[1] In comparison, in the case of complete small bowel obstruction such as duodenal atresia or volvulus, most patients present with acute and severe signs and symptoms of obstruction such as profuse bilious vomiting.

The etiology of duodenal obstruction can be classified as intrinsic or extrinsic based on the source of blockage.[2] Intrinsic duodenal obstruction refers to duodenal atresia, duodenal stenosis and duodenal webs.[3] The mechanism behind this is thought to be due to failure of the duodenal lumen to recanalize during fetal development, which occurs at roughly 8-10 weeks in utero.[3] On the other hand, extrinsic duodenal obstruction may occur due to malrotation, midgut volvulus, annular pancreas or any other external organs that compress the lumen of duodenum. [4]

For clinicians, initial evaluation of children with suspected bowel obstruction should focus on differentiating whether the cause of that obstruction is an emergency or not, to avoid further devastating consequences. Therefore, this case report aims to describe the atypical case of pediatric duodenal stenosis which presented with recurrent vomiting and poor weight gain as well as highlight some of the diagnostic challenges.

Case

A 7-month-old girl was admitted to the emergency room with chief complaint of recurrent vomiting in the last 2 days prior to hospital admission. Complaint was also accompanied by fever that started 1 day prior to admission. Vomiting occurred with a frequency of 4-5 times per day, which consisted of milk, white in color with no clumping. Parents reported that the patient vomited about as much as 1 aqua cup during the first episode of vomiting and then half aqua cup at the second episode of vomiting.

According to the patient's mother, fever was not immediately high, although it was not properly measured, and continued throughout the day with no temperature fluctuation. She also noticed that her child had watery stool 1 day prior to admission with a frequency of 4 times a day and as much as half aqua cup for each bowel movement. Stool was characterized as brown in color with foul odor which was different than usual, but without any mucous or blood. According to the patient's mother, the patient could still drink but the patient looked very thirsty. In the

emergency room after the patient was given fluids through IV access, the patient didn't seem thirsty anymore.

Patient had a history of recurrent bilious vomiting at the age of 3 days old with a frequency of 3-4 times a day and were admitted to the hospital for 2 weeks. Parents also reported of poor weight gain in the last 3 months.

On physical examination, patient was fully conscious but looked moderately ill. Vital signs were normal. Patients had malnutrition with body weight of 6 kg and body length of 66 cm (z score for weight-for-length <-2 SD). Nothing remarkable during inspection of the abdomen, however pain was felt during palpation with no organomegaly. No shifting dullness was observed during abdominal percussion. Bowel movement was 6 times per minute.

Upon laboratory evaluation, hypochromic microcytic anemia, leukocytosis and thrombocytosis were found (**Table 1**).

Table 1. Laboratory results from the patient

Parameters (Unit)	Value	Reference Value
Hemoglobin (g/dL)	10.6	10.5-14.0
Hematocrit (%)	33.3	32-42
Erythrocyte (10^6/µL)	4.58	3.95-5.26
MCV (fL)	72.7	72-88
MCH (pg)	23.1	24-30
MCHC (%)	31.8	32-36
Thrombocyte (10^3/mm^3)	609	150-400
Leucocyte (10^3/mm^3)	18.85	6-14
Neutrophil (%)	77.7	25-60
Monocyte (%)	6.8	2-8
Lymphocyte (%)	9.1	20-40
Eosinophil (%)	6.2	1-3
Basophil (%)	0.2	0-1
ESR	25	0-20
Calcium ion (mmol/L)	1.02	1.01-1.31
Phosphate (mg/dL)	6.3	2.5-7.0
Magnesium (mg/dL)	2.03	1.70-2.55

Two days after being treated, complaints of watery stool improved but the patient still experienced repeated profuse vomiting 3-4 times a day. Abdominal X-Ray with contrast was performed (**Figure 1**). Patient was then consulted to pediatric surgeon. Upon esophageal endoscopic evaluation, severe GERD with a pyloric gap was found

as well as a suspicion of a duodenal web (**Figure 2**). The patient was then planned for laparotomy correction of duodeno-duodenostomy. Patient was then treated with cefotaxime 150 mg three times a day, paracetamol 75 mg four times a day and intravenous fluid.

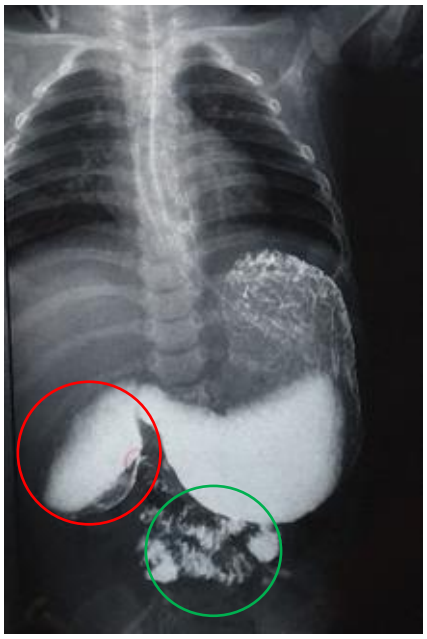

Figure 1. Abdominal X-Ray series showed dilatation of the small intestines immediately after pylorus (red circle) and stack of coins sign (valvulae conniventes) distal to the dilatation part (green circle).

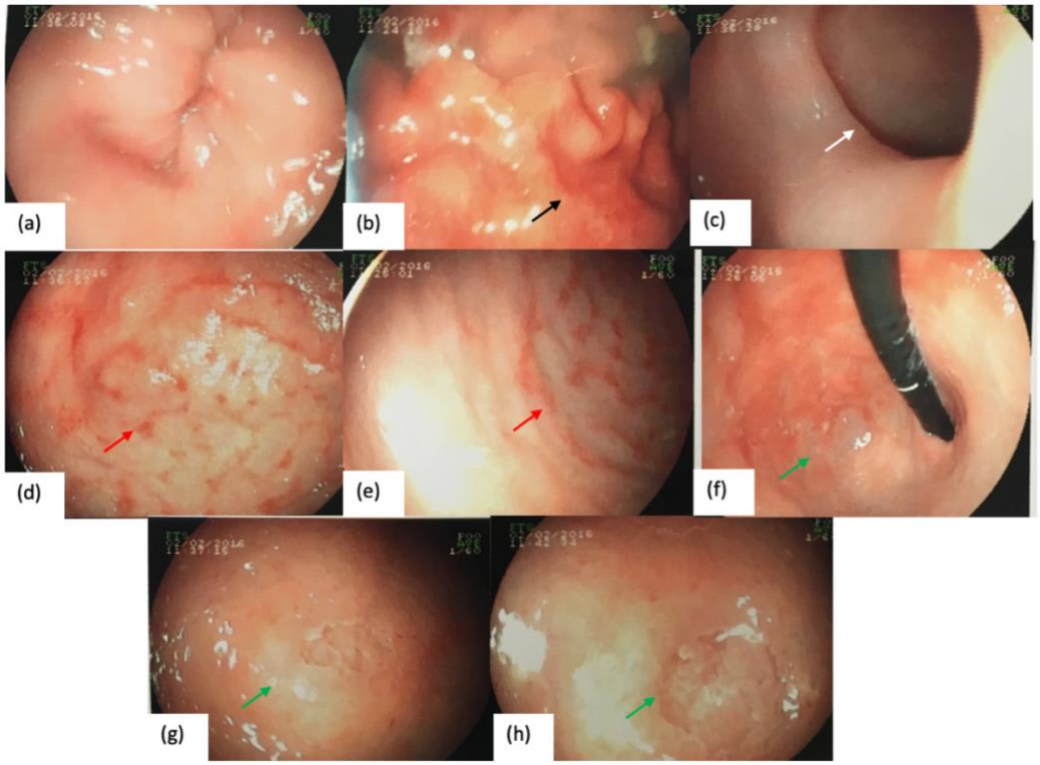

Figure 2. (a) Esophageal mucosa was normal. **(b)** Mucosa of the gastric corpus, cardiac and fundus showed remarkable hyperemia, erosion and gastropathy (black arrow). **(c)** Wide opening of the pylorus (white arrow). **(d), (e)** Mucosa of the duodenum was hyperemic with extensive erosion and fragile (red arrows). **(f), (g), (h)** Lumen of the duodenum was blocked by mucosal fold which prevented the scope to pass through (green arrows).

Discussion

Duodenal stenosis, along with duodenal atresia, is a congenital intestinal obstruction that leads to bilious or non-bilious vomiting within the first 24 to 72 hours of neonatal life, following the first oral feeding.[1,5] Duodenal stenosis and duodenal atresia is the most common cause of intrinsic congenital duodenal obstruction which occurs 1 in 5000 to 10,000 live births.[5]

Congenital obstruction at the duodenum may occurs due to intrinsic or extrinsic etiology. Intrinsic duodenal obstruction can be caused by duodenal atresia, duodenal stenosis, and duodenal webs. On the other hand, extrinsic duodenal obstruction can be caused by malrotation with Ladd's bands or by the presence of the preduodenal portal vein.[1,6]

Failure of duodenal re-canalization during the 8-10th week of embryological development is the main cause of duodenal atresia. It usually occurs at the distal of the ampulla of Vater, in the second portion of the duodenum.[5] Duodenal atresia

occurs when the duodenum is not completely formed which results in a complete obstruction of the duodenal lumen. In duodenal stenosis, the lumen is narrowing, resulting in an incomplete obstruction of the duodenum lumen. These anomalies are frequent in newborns and patients with chromosomal abnormalities, such as Down syndrome.[7] A duodenal web is a more rare cause of duodenal obstruction, in which the duodenal lumen tends to have a windsock deformity.[5,6] In this case, there was no evidence of an extrinsic obstruction.

Manifestation of duodenal stenosis appears within 24 to 72 hours after birth, in which the age of presentation depends on the degree of stenosis itself. The presentation may appear later compared to duodenal atresia due to more distal blockage, hence abdominal distension and vomiting were the most common features.[1] Vomiting occurs due to an obstruction in the upper digestive tract, hence the breast milk or amniotic fluid that pass through the stomach cannot proceed to the duodenum, thus resulting in vomiting a few hours after birth.[6] Clinical presentation may vary from repeated vomiting, gastric distension, failure to thrive in infancy, gastroesophageal reflux and peptic ulcer which depends on the age of the patients. Poor weight gain, signs of dehydration, minimal or no stool may also present.[1,7,8] This patient came to our hospital due to recurrent vomiting for two days, 4-5 times a day, with white in color without any lumpy texture. However, this patient also had a history of being treated for two weeks in the hospital due to recurrent vomiting within the first 72 hours of life, with bilious vomitus as frequent as 3-4 times. No other symptoms or abnormalities were recorded at birth. The presence of bilious emesis indicates duodenal atresia or stenosis. Obstruction distal to the ampulla of Vater results in a greenish color of bile mixed with vomit that comes out. The symptoms that appear depend on the location of the obstruction itself. Proximal obstruction of the intestinal tract may present as frequent bilious vomiting with large volume. Meanwhile, the distal obstruction is indicated by moderate abdominal distention with progressive vomiting. Patients with duodenal atresia or stenosis may develop dehydration when vomiting persists. It is also necessary to look for signs of dehydration such as sunken fontanels, reduced or even absent tears, dry oral mucosa, slowed skin turgor, and if the baby is looking weak and apathetic.[6] Our patient showed dehydration symptoms, in which she looked very thirsty when she first came. The symptom improved after adequate rehydration was given. The patient's body weight increased up to 3 months old, yet decreased afterward. Patient also suffered from malnutrition at the time of admission. Although there was some notable weight loss, this might also be related with previous hospitalization episode due to septic shock, meningitis, history of seizure, and loss of consciousness. Our patient also showed delayed in developmental milestones which needed further evaluation.

On inspection, abdominal distension may be seen, indicating distal obstruction. On palpation examination, the stomach in the epigastric area might feel enlarged.[6] Our patient showed flat abdomen on inspection, which might be due to previously installed nasogastric tube, resulting in decompression.

Laboratory findings may show hemoconcentration suggesting dehydration. Hypokalemia or hypochloremic metabolic alkalosis can also be found due to repetitive vomiting.[1,6] However, in this case, only leukocyte, neutrophil, lymphocytes, and erythrocyte sedimentation rate increased. Leukocytosis may be related with fever and diarrhea that presented 1 day before hospital admission in this patient. Other findings were within normal limits.

Duodenal stenosis may present with polyhydramnios or dilated loops of bowel on fetal sonography during prenatal period. Extrinsic duodenal obstruction such as annular pancreas, duplication cyst, and preduodenal portal vein as well as pyloric stenosis need to be ruled out in postnatal ultrasound.[1] None of these findings were showed in our cases.

Plain abdominal radiograph has been used as the first step for duodenal stenosis evaluation. The double bubble sign with the absence of distal intestinal gas indicates duodenal stenosis or atresia.[1,6,8] The first bubble indicates the presence of fluid filling in the gastric area. The second bubble indicates the distended post-pyloric/proximal duodenum which is located before the site of atresia or stenosis. No visible air in the rest of the small intestine or large intestine suggests duodenal atresia (complete obstruction), meanwhile, an uneven distribution of air in the distal part of the obstruction suggests the possibility of stenosis or volvulus (partial obstruction). Radiological examination using contrast is used to rule out the possibility of malrotation.[6] In this case, the patient's abdominal x-ray revealed a dilatation of the intestinal area after the pylorus and valvula conniventes (a stack of coins after the area is dilated). In addition, the results of esophagogastroduodenoscopy showed severe gastroesophageal reflux, gastropathy, pyloric gap, and suspected duodenal web. A duodenal web is a rare cause of duodenal obstruction, which tends to cause a windsock deformity of the duodenal lumen.[5] Hence, it is concluded that the main symptoms of our patient were caused by an intestinal obstruction at the level of the duodenum due to duodenal stenosis.

The management of duodenal stenosis involves several aspects. Fluid administration needs to be given according to the degree of dehydration. Decompression is done by inserting a nasogastric or orogastric tube.[6,8] Nutrition can be given parenterally according to the needs of the patient pre- and post-surgery. Gastric residual is usually monitored after the surgery. Electrolytes should be monitored, especially when

dehydration occurs. The optimal temperature also needs to be maintained. The definitive treatment of duodenal atresia or stenosis is surgery to resect the obstructed part and connect the remaining part of the digestive tract with an anastomosis.[6] The recommended surgical procedure is the duodeno-duodenostomy in which the proximal and distal sections of the duodenum are connected after resection of the obstruction site[6-8], which was performed in our patient. In this case, the fluid administration was immediately given when the signs of dehydration were found. The decompression had also been carried out by inserting a nasogastric tube. Antibiotics and antipyretics were also given.

Conclusion

Congenital duodenal stenosis may present with atypical presentations in neonates which requires clinicians to be fully aware of this diagnosis to ensure timely therapy. Diagnosing duodenal stenosis is often challenging as this disease causes partial intestinal obstruction and thus presents with more indolent and atypical clinical manifestations. Plain abdominal radiograph as well as series abdominal X-Ray with contrast are beneficial to confirm the diagnosis of duodenal stenosis as well as to exclude other differential diagnosis particularly those from extrinsic source. The main management of duodenal stenosis is surgery, however fluid administration, decompressing as well as other supportive treatment are equally crucial to ensure better outcome for the patient.

Conflict of Interest

None declared.

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Literature Review

How to Interpret Liver Function Test in Daily Practice

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Abstract:

Background: The liver is a multi-function organ that plays a role in producing various important secrete, synthesis and metabolic functions. The term liver function test is also used to refer to the hepatocyte synthesis function, such as serum albumin and prothrombin time. The aim of this literature review is to explain on how to interpret various liver function test results in daily practice as well as approach to abnormal liver function tests.

Discussion: Abnormal result of liver function test is frequently found in asymptomatic healthy patients who are undergoing routine screening. On the contrary, some patients with liver disease may appear with normal liver function test. As such, there are some limitations regarding this particular test. Alanine aminotransferase is the primary marker of hepatocellular injury due to it being more sensitive and specific than aspartate aminotransferase. Conjugated bilirubin level of more than 20% of total bilirubin level is a strong indication of hepato-biliary disease and is always pathogenic. Gamma-glutamyl transferase (GGT) is only increased in cholestatic conditions and not in bone disease. As such, GGT levels can help to distinguish abnormalities in the liver or bones in conditions of increased alkaline phosphatase levels in the blood.

Conclusion: Serum liver biochemistry examination is very useful and effective in assessing liver function. Understanding the proper interpretation of liver enzymes will help clinicians easier to diagnose or predict a disease as well as condition related to the liver in daily practice.

Keywords: interpretation, liver enzyme, liver function test, pediatric

Introduction

The liver is a multi-function organ that plays a role in producing various important secrete, synthesis and metabolic functions. Although in general, the term liver function test is often used, this term actually consists of various types of tests that evaluate not only the liver function but also other essential aspect of the liver, such as transaminase which is an indicator of liver cell destruction.[1] The term liver function test is also used

to refer to the hepatocyte synthesis function, such as serum albumin and prothrombin time. However, in certain circumstances, liver biochemical tests may produce normal values in patients with liver disease such as in compensated cirrhosis as well as abnormal results in healthy children.[1] In this literature review, we will discuss how to interpret various liver function test results in daily practice as well as approach to abnormal liver function tests.

Liver Function Test

Abnormal result of liver function test is frequently found in asymptomatic healthy person who are undergoing routine screening.[2] On the contrary, some patients with liver disease may appear with normal liver function test. As such, there are some limitations regarding this particular test such as:

1. Normal result of liver function test does not always indicate that the patient does not have liver disease especially in the case of compensated cirrhosis.
2. Some tests do not specifically assess liver function
3. The tests performed do not show a specific etiology but indicate a liver disorder in general, so interpreting any abnormal liver test result must be done case-by-case and may differ for each patient.

There are five categories of liver function tests that evaluate specific aspect of the hepato-biliary system[3,4]:

1. Liver injury markers which include liver enzymes such as aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT).
2. Cholestasis markers such as alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and 5'-nucleotidase.
3. Synthesis function markers such as serum albumin, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR) and coagulation factor V as well as VII.
4. Excretion function markers which include bilirubin level and bile acid.
5. Liver metabolism function markers which depict the detoxifying role of the liver and the clearance mechanism of endogenous metabolites such as ammonia.

Based on the categories described earlier, liver enzymes such as AST and ALT which are commonly examined in patients with liver disease, actually do not indicate specific liver function disorders but only show the presence of liver damage.[5,6] As of now, there is no direct relationship between those enzyme levels with the degree or severity of liver damage. Normally, AST and ALT are found in serum at low levels in the healthy population. Evaluation of liver biochemistry test is very useful and provide

the most cost-effective way of assessing liver function. This examination is also routinely performed on asymptomatic people for routine screening, blood banks screening, examinations for insurance purposes, or patients who will perform surgical procedures that are not directly related to liver function.[3] The liver function tests that are commonly evaluated are alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALP), prothrombin time (PT), serum albumin, gamma-glutamyl transferase (GGT), bile acids, 5'-nucleotidase, and lactate dehydrogenase.[1]

Liver Enzyme

Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)

Serum ALT or SGPT is one of the oldest markers used to assess liver disease. This substance is a cytosolic enzyme that is found in high concentrations in the liver and also in the kidneys, heart, muscle, pancreas, spleen, and lung tissue.[1,3,7] Thereby, increased level of ALT do not always indicate liver disease but may be caused by myocardial infarction, muscular dystrophy, and organ damage.[3] This enzyme is a useful serum for measuring liver function because of its high sensitivity and specificity (increase of 2.25 times greater than normal levels predict the presence of liver histological abnormalities). Nevertheless, ALT serum levels are influenced by many other factors, including gender, body mass index, and the use of hepatotoxic drugs.[8,9] Moreover, a strong relationship was found between ALT and body mass index (BMI). The American Society of Gastroenterology categorizes ALT levels according to the degree of elevation with several differential diagnoses based on the probable cause of liver damage (**Table 1**).[3]

Table 1. Degree of Elevation of ALT Level and Possible Etiology.

Mild elevation (<5 times of upper normal limit)	Severe elevation (>15 times of upper normal limit)
Chronic hepatitis B and C	Acute hepatitis (A, B, C, D, E, herpes)
Acute hepatitis (A, B, C, D, E, EBV, CMV)	Drugs or toxins
Steatohepatitis	Ischemia hepatitis
Hemochromatosis	Autoimmune hepatitis
Drugs or toxins	Wilson disease
Autoimmune hepatitis	Acute obstruction of the biliary duct
Alpha-1 antitrypsin deficiency	Budd-Chiari syndrome
Wilson disease	Ligation of the hepatic artery
Celiac disease	
Liver injury due to alcohol	
Cirrhosis	
Non hepatic (hemolytic, myopathy, thyroid disorders)	

In a study conducted at LabCorp America, the normal values of ALT level were categorized based on age and gender (**Table 2**).[3,10]

Table 2. Normal ALT Value Based on Gender and Age in Pediatric

Gender	Age Interval (years)	ALT/SGPT Level (U/L)
Female	0-11	< 29
	12-17	< 25
	≥ 18	< 33
Male	0-11	< 30
	12-17	< 31
	≥ 18	< 45

The ALT is the primary marker of hepatocellular injury due to it being more sensitive and specific than AST .[11] There are several etiologies that may lead to an increase in ALT level such as[11]:

a. Highly elevated ALT level (> 15-20 times of upper normal limit)
   - Ischemia (shock, hypotension, congestive heart failure)
   - Viral hepatitis, autoimmune hepatitis
   - Drug toxicity, severe toxic hepatitis
   - Acute Budd-Chiari syndrome

b. Moderately elevated ALT level (5-15 times of upper normal limit)
   - Liver disease: chronic liver disease (chronic hepatitis, cholestasis with increase in ALP and GGT)
   - Cardiac disease: severe hepatic congestion due to congestive heart failure
   - Other: muscle injury, kidney injury

c. Mildly elevated ALT level (<5 times of upper normal limit)
   - Liver disease: neonatal hepatitis, hemochromatosis, autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), biliary atresia, alpha-1 antitrypsin deficiency and Wilson disease.
   - Infection: Mononucleosis
   - Drugs: anti-tuberculosis, anti-epileptic, antibiotics and non-steroid anti-inflammatory drugs (NSAID).

d. False low ALT level such as patient who undergo dialysis or deficiency in pyridoxin.

Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)

Aspartate Aminotransferase is found in both cytosolic and mitochondrial isoenzymes, and is also found in high concentrations in various tissues such as liver, heart muscle,

skeletal muscle, kidney, brain, pancreas, lung, leukocytes and red blood cells.[10,11] Normally, low concentration of AST is found in the blood, unless there is cellular injury, then large amounts are released into the circulation.[11]

Aspartate Aminotransferase enzymes can greatly increase in serum during conditions of increased tissue metabolism. If disease or damage occurs to one of these cells, the cell will lyse and consequently AST enzyme will be released into the circulation causing the serum level to increase.[11,12] The normal value of serum AST is 20-60 U/L in infants, <45 U/L (boys), and <30 U/L (girls) (**Table.3**).[13] Serum AST will increase 8 hours after damage occurs, with a peak at 24 to 36 hours after damage and returns to normal within 3 to 7 days. If the damage is chronic then the increase will persist. This increase in the AST enzyme indicates liver cell damage, but is less specific for liver disease.[11-13]

An increase in AST can be caused by[11]:

a. High increase in AST level (>20 times of upper normal limit)
   - Ischemia (Shock, hypotension, Congestive Heart Failure,)
   - Acute viral hepatitis
   - Drug Induced Hepatitis

b. Moderate increase in AST (15-20 times of upper normal limit)
   - Cardiovascular system: congestive heart failure
   - Infection: infectious mononucleosis
   - Liver: alcoholic cirrhosis

c. Slight increase in AST (5-10 times of upper normal limit)
   - Liver: chronic hepatitis (alcoholic)
   - Muscle: duchenne muscular dystrophy, dermatomyositis

d. Very mild increase in AST (< 5 times of upper normal limit)
   - Blood: Hemolytic Anemia, Hemolysis
   - Liver: Fatty liver, liver tumor metastases
   - Others: Acute pancreatitis
   - Drugs: various types of drugs

Table 3. Aspartate Aminotransferase level in infants and children based on age.[13]

Age	AST level, both genders (U/L)	Age	AST Level (U/L)	
			Male	Female
0-5 day	35-140	10-11 yrs	10-60	10-40
6 days–3 yrs	20-60	12-15 yrs	15-40	10-30
4-6 yrs	15-50	16-18 yrs	10-45	5-30
7-9 yrs	15-40	≥ 19 yrs	17-59	14-36

In the following algorithm below from Lab Corp America, a clinical and laboratory assessment can be carried out for very mild increases in ALT and/or AST serum (**Figure 1**).[10,14]

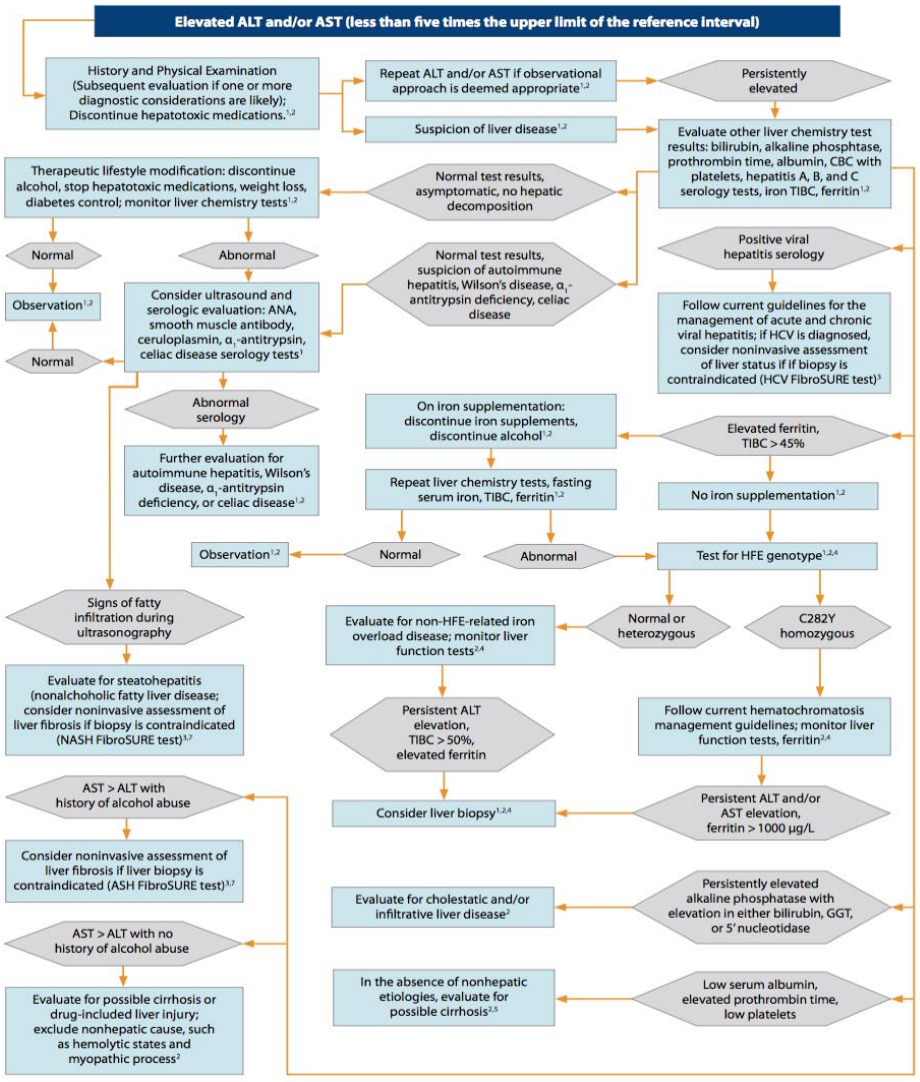

Figure 1. Algorithm for clinical and laboratory evaluation in the case of very mild increase in serum ALT and/or AST.[10,14]

Bilirubin

Conjugated bilirubin level of more than 20% of total bilirubin level is a strong indication of hepato-biliary disease and is always pathogenic. This is often accompanied by the presence of bilirubin in the urine (causing dark yellow urine) which can also be detected using a dipstick. Bilirubinemia may also be accompanied by clinical jaundice. In cases of acute liver disease that is not accompanied by jaundice (anicteric), it is still possible for the patient to experience fulminant liver failure

accompanied by much later increase in bilirubin levels. As such, serum bilirubin can serve as a prognostic indicator in patients with acute liver diseases.[1]

Table 4. Bilirubin level in infants and children based on age.[13]

Age	Bilirubin level (mg/dL)	
	Premature Total	**Full Term Total**
Up to 23 h	1-8	2-6
24-48 h	6-12	6-10
3-5 days	10-14	4-8
≥1 month		
Conjugated bilirubin	<0.35	
Unconjugated bilirubin	<1.0	
Total	0.2-1.0	

The normal value of conjugated bilirubin for children is 0.0-0.2 mg/dL (**Table.4**).[13] Cholestasis is a condition of which marked by the failure of the bile to flow into the duodenum in normal amounts. Disturbances of the bile flow can occur anywhere from the basolateral membrane of the hepatocytes to the site of entry of the bile duct into the duodenum.[15] The obstruction of the bile flow causes retention of various substances that should be excreted into the gallbladder with direct bilirubin level 1.0 mg/dL if total bilirubin is under 5 mg/dL or direct bilirubin above 20% of total bilirubin if total bilirubin level is above 5 mg/dL.[16]

Based on the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition indicators of cholestasis are[17]:

- Direct bilirubin >17μmol/L (1.0 mg/dL)
- Direct bilirubin >20% of total serum bilirubin concentration, if total bilirubin >85μmol/L (5.0 mg/dL)

Currently, the most recent definition of cholestasis is defined when the direct bilirubin level is >1.0 mg/dL.

Gamma-Glutamyl Transferase (GGT)

The enzyme gamma-glutamyl transpeptidase-1 (GGT-1, gamma-GT, gamma-glutamyl transferase) is used as a disease diagnostic marker (**Figure 2**). Gamma-glutamyl transferase (GGT) is a membrane glycoprotein that catalyses the transfer of gamma-glutamyl to other peptides, amino acids or water.

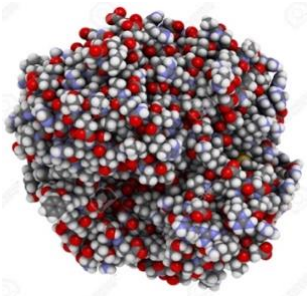

Figure 2. Gamma-glutamyl transpeptidase-1[18]

Large amounts of gamma-glutamyl transferase can be found in the kidneys, pancreas, liver, small intestine, and prostate. In the kidney, GGT is abundant on the luminal surface of proximal tubular cells. Meanwhile, in the liver, GGT is abundant in bile epithelial cells and bile canaliculi, GGT is also found in acinar cells of the pancreas, endothelial cells lining the brain, spinal cord, and cells in the male reproductive organs. Gamma-glutamyl transferase which present in astrocyte cells in the blood vessels of the brain has a role in the blood-brain barrier, both in conjugating toxic xenobiotics and metabolizing leukotrienes. GGT can also be found in white blood cells. The function of GGT on white blood cells is still unclear. However, there are two theories which state that GGT protects white blood cells from free radicals, especially during inflammatory processes and helps modify the interaction between receptors and ligands on cell membranes.[1,19,20]

Gamma-glutamyl transferase is mainly found in organs that have transport function such as the kidney and the biliary system. GGT plays a major role in helping to synthesize glutathione. The specific relationship between GGT and glutathione and the response of GGT to excessive alcohol consumption has led to GGT being used as a marker of excessive alcohol consumption.[19,20]

Gamma-glutamyl transferase levels are high in neonates, infants up to 1 year of age, and at >60 years of age. Men have higher GGT levels than women. Normal levels of GGT are 0-30 IU/L.(**Table 5**).[13] During acute viral hepatitis infection, GGT levels will reach their highest levels in the 2nd and 3rd weeks and remain high for 6 weeks. In extrahepatic biliary atresia, GGT levels are also increased. GGT is only increased in cholestatic conditions and not in bone disease. As such, GGT levels can help to distinguish abnormalities in the liver or bones in conditions of increased ALP levels in the blood.[1,19,20]

Table 5. Gamma-glutamyl transferase level in infants and children based on age.[13]

Age	GGT level, both genders (U/L)	Age	GGT Level (U/L)	
			Male	Female
0-5 day	34-263	10-11 yrs	17-30	17-28
6 days–2 months	10-160	12-13 yrs	17-44	14-25
3-11 month	11-82	14-15 yrs	12-33	14-26
1-3 yrs	10-19	16-18 yrs	11-34	11-28
4-6 yrs	10-22	≥ 19 yrs	10-78	10-78
7-9 yrs	13-25			

Other conditions associated with elevated GGT levels are uncomplicated diabetes mellitus, acute pancreatitis, and myocardial infarction. Drugs such as phenobarbital, phenytoin, paracetamol, tricyclic antidepressants can also increase GGT levels. [1,19,20] The reference range for normal GGT values is the same for all ages. However, there are significant differences between men and women. Several other factors also affect the normal value of GGT in serum, such as age, sex, pregnancy, childbirth, race, smoking habits, use of oral contraceptives, and exercise. [1,19,20]

Serum GGT levels are found to be abnormal in liver disease, suggesting that GGT liver function test are sensitive. The highest increase in serum GGT levels was found during conditions of liver inflammation due to excessive alcohol consumption or in conditions of liver inflammation due to drug consumption. However, increased levels of GGT in serum are not specific for liver disease because these increases are also found in conditions of excessive alcohol consumption, pancreatitis and obesity. Serum GGT levels also increase in chronic liver disease associated with hepatitis C infection. Hence, the use of GGT levels in predicting the body's response to interferon administration in individuals with hepatitis C infection have been widely studied. The results showed that GGT levels had a sensitivity of 87% but a specificity of only 27%.[19,20]

Alkaline Phosphatase (ALP)

Alkaline phosphatase (ALP) is found in a number of tissues including the canalicular membranes of hepatocytes, bone osteoblasts, small intestinal enterocytes, proximal renal tubules, placenta, and white blood cells. ALP is an enzyme synthesize by the cell wall of the bile canaliculi in response to intra- or extrahepatic cholestasis. This enzyme serves as the primary marker of cholestatic disorders before bilirubin level increases. The function of ALP many are unknown, but it plays a role in the transport process. Serum ALP levels often vary with age. Furthermore, ALP is a zinc metalloenzyme group and is present in almost all tissues. In the liver, ALP is present in microvilli along the bile duct canaliculi and on the surface of the hepatocyte sinusoids. The ALP

found in the liver, bone and kidney originate from the same gene, but the ALP found in the small intestine and placenta originate from different genes. ALP can be detected in serum, urine, bile salts, and lymphatic fluids.[1,11,21]

In healthy person, ALP circulating in the blood originates from the liver or bones. This enzyme levels are relatively higher during childhood and puberty. ALP levels are directly proportional to body weight but inversely proportional to height. The highest ALP levels were found in cholestatic conditions. An increase in ALP occurs due to obstruction to the intrahepatic or extrahepatic flow of bile salts. The mechanism by which ALP is released into the blood is still unknown. There is a theory that damage to the tight junctions in the bile salt canaliculi causes the release of ALP into the hepatocyte sinusoids. Normal ALP level in children is 39-117 U/L (**Table 6**).[13] Elevated levels of ALP indicate a biliary obstruction (intrahepatic and extrahepatic), biliary atresia or viral hepatitis.[1,11]

Table 6. Alkaline phosphatase level in infants and children based on age.[13]

Age	ALP level, both genders (U/L)	Age	ALP Level (U/L)	
			Male	Female
0-5 day	110-300	10-11 yrs	135-530	130-560
6 days–11 months	110-320	12-13 yrs	200-495	105-420
1-3 yrs	145-320	14-15 yrs	130-495	70-230
4-6 yrs	150-380	16-18 yrs	65-260	50-130
7-9 yrs	175-420	≥ 19 yrs	38-126	38-126

In acute viral hepatitis infection, ALP levels may be normal or slightly elevated. During hepatitis A infection, cholestatic conditions can be found which are characterized by itching and increased levels of ALP. On the other hand, tumors can also release ALP into the plasma. Elevated levels of ALP from the small intestine can be found in cirrhotic conditions that are associated specifically with intrahepatic disease. Other conditions that may be associated with elevated ALP levels include bone and liver metastases, infiltrating liver disease, abscesses, granulomatous liver disease, and amyloidosis.[11,21] Mild elevations in ALP levels can be found in cirrhosis and hepatitis with congestive heart failure. Low ALP levels in the blood can be found in conditions of malnutrition, hypothyroidism, pernicious anemia, zinc deficiency, vitamin C deficiency and congenital hypophosphatemia.[11,21]

If the serum ALP level increases but is less than 1.5 times of the upper normal limit, then a reexamination must be carried out 3 months later. If the serum ALP level is more than 1.5 times of the upper normal limit and persistently elevated, it is necessary to carry out additional investigations such as ultrasound of the liver to detect

cholestasis or other infiltrating disease. If the examination results are normal and the serum ALP increases to less than 1.5 times of the upper normal limit, then a re-examination should be carried out 6 months later. However, if the serum ALP level increases to more than 1.5 times the upper normal limit and ultrasound as well as serological examinations produce normal results, then the patient should be referred to a hepatologist for a liver biopsy.[21]

If an increase in serum ALP level is found but the GGT level is normal, this indicates that the increased ALP level originates from tissues outside the liver and most likely originates from the bone due to vitamin D deficiency. Therefore, it is necessary to check blood levels of vitamin D. If the vitamin D level is within normal limits and the increase in ALP level is less than 1.5 times of the upper normal limit, then the patient should only be observed.[21,22]

The following is an algorithm to evaluate the presence of elevated ALP in the blood (**Figure 3**).[21]

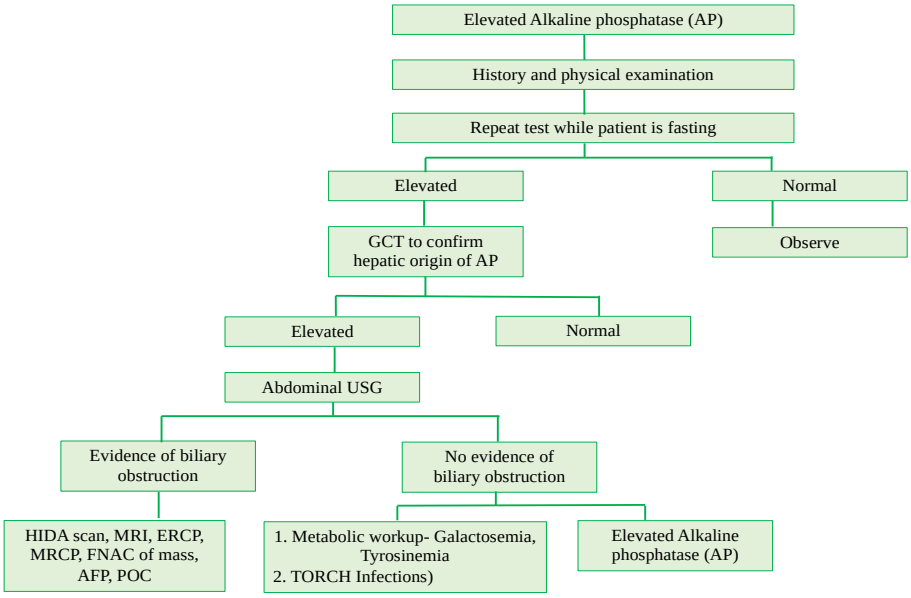

Figure 3. Algorithm for evaluation of increased alkaline phosphatase.[21]

Serum Protein

Albumin

Albumin is a serum protein and is only synthesized in the liver. This protein is synthesized in the endoplasmic reticulum of hepatocytes at a rate of 150 mg/kg/day and has a life span of about 20 days in serum. Taking into account the length of life span, low serum albumin indicates a chronic liver disease.[1] The normal value of albumin in children is 3.5-5.5 g/dL.[13] In a state of liver disease with an increase in

globulin level but normal albumin level, indicates the presence of infectious process or autoimmune hepatitis. However, in patients with compensated liver disease, serum albumin can be found to have normal values. Hypo-albumin is not specific for liver disease because it can also occur in malnutrition, protein losing enteropathy, chronic infections and nephrotic syndrome.[1]

Coagulation Factors

Coagulation disorders are found in patients with liver disease due to disorder of hepatic synthesis of coagulation factors V, VII, IX, X and XI prothrombin, fibrinogen as well as vitamin K deficiency due to inadequate intake or malabsorption and dysfibrinogenemia. Coagulation disorders is often so subtle during mild or moderate liver disease. However, it is often found severe during acute hepatic failure or terminal chronic liver disease.[1]

Increase of Liver Enzymes Due to Non-Hepatic Etiology

In certain circumstances, liver enzymes can increase due to abnormalities other than liver disease. If liver disorders have previously been ruled out but liver enzymes are found to be elevated, it is necessary to consider and investigate abnormalities caused by disorders of the muscles, heart, thyroid disease, celiac disease, and, rarely, insufficiency of adrenals. Conditions of increased muscle injury with increased transaminase enzymes may also be accompanied by increased creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). If an elevated ALT and AST condition persist for more than three months, exceeds two times of the normal value and the results of other tests do not produce clear conclusion, then it is necessary to recommend liver function tests.[1]

Conclusion

Serum liver biochemistry examination is very useful and effective in assessing liver function. The tests that are commonly evaluated include alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase, prothrombin time, serum albumin, gamma-glutamyl transferase (GGT), bile acids, 5'-nucleotidase, and lactate dehydrogenase. Understanding the proper interpretation of liver enzymes will help clinicians easier to diagnose or predict a disease as well as condition related to the liver in daily practice.

Conflict of Interest

None declared.

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