

Analysis of common causes of liver damage among children 12 years and younger in Weifang

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Abstract

Aims: To explore the causes of liver damage among children 12 years and younger in Weifang and to provide a theoretical basis for early diagnosis of liver damage in children.

Methods: Retrospective study of clinical data from pediatric patients (age ≤ 12 years) with liver damage in diagnosed at Weifang People's Hospital from June 2010 to May 2020.

Results: A total of 2632 children (1572 boys, 1060 girls) aged ≤ 12 years were diagnosed with liver damage including infectious liver damage (2100 cases), non-infectious liver damage (446 cases) and liver damage of unknown etiology (86 cases). The most common causes of infectious liver damage were viral infection (1515 cases), *Mycoplasma pneumoniae* infection (343 cases), and bacterial infection (197 cases). The most common causes of viral liver damage were Epstein–Barr virus, cytomegalovirus, and enterovirus. The most common causes of non-infectious liver damage were drug-induced liver damage, Kawasaki disease, and genetic metabolic diseases. There were 31 cases of severe liver damage.

Conclusion: There were many causes of liver damage among children in Weifang. Infections, and especially viral infections such as Epstein–Barr virus, were the most common causes of liver damage. Severe liver damage was primarily caused by drugs or poisons.

Keywords

Liver damage, etiology, alanine aminotransferase, viral infection, children, Epstein–Barr virus

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Introduction

Because children are actively growing and developing, their immature livers are easily affected by various endogenous and exogenous factors that can lead to liver damage. The causes of liver damage are numerous and complex. Different countries and regions have different spectra of disease,¹ and children of different ages can have different disease characteristics. Liver damage can be a separate disease or a complication of another condition. Because of the multiple complex causes of liver damage, previous studies of liver damage in children were mostly limited to short periods of time or to a specific age group.²⁻⁴ Systematic and detailed studies are lacking. Therefore, it is necessary to conduct more detailed investigations of the causes of liver damage among children living in a defined area over a longer period. These data could document epidemiological characteristics and trend in liver diseases.

Weifang is in the central part of Shandong Province, where the inland and peninsulas of Shandong Province meet. It has a population of 10 million. The administrative area and population of Weifang rank second in Shandong Province. The incidence and epidemiologic trends of childhood liver disease in Weifang are representative of those of Shandong Province. Weifang People's Hospital is the largest tertiary first-class hospital in Weifang and a provincial-level regional medical center in Shandong. The hospital provides the highest level of pediatric medical care and diagnostic capacity in Weifang.

There are many indicators of liver damage, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamate transpeptidase, total bile acid, albumin, total bilirubin, and indirect bilirubin. Elevated ALT and AST are the most commonly used markers of liver damage. ALT

is mainly present in the cytoplasm, while AST is mainly present in the mitochondria. Generally, mild to moderate liver damage is manifested as an increase in ALT, whereas severe liver damage is often accompanied by an increase in AST and the AST/ALT ratio.⁵ ALT is the most sensitive indicator of liver damage. Damage to 1% of liver cells can cause a two-fold increase in ALT. Therefore, in clinical practice, increased ALT is usually the most important manifestation of liver damage.⁶ Because children's bones are growing and developing, ALP levels are generally high. Therefore, it is inappropriate to use ALP as an indicator of pediatric liver damage, as this is neither a specific nor sensitive biomarker.

This study aimed to retrospectively summarize and analyze the causes of liver damage among children aged ≤ 12 years diagnosed at Weifang People's Hospital over the past 10 years. We hoped to clarify common causes and epidemiologic trends in liver damage among children in the Weifang area. These data may provide a theoretical basis for clinical research and enable early interventions for pediatric liver damage.

Methods

Patient selection

We searched the electronic database of outpatient and inpatient medical records of Weifang People's Hospital. Patients aged ≤ 12 years who were diagnosed with liver damage in the Pediatric Department of Weifang People's Hospital from June 2010 to May 2020 were identified. We performed a retrospective study of all medical records. The study was approved by the Ethics Committee of Weifang People's Hospital (approval number: 2020321) and followed the Equator network guidelines. As a retrospective study of anonymized medical

records, the requirement for informed consent was waived.

At present, there are no uniformly standardized criteria for diagnosis of liver damage. Clinically, fasting venous blood ALT >80 U/L (chemiluminescence method, normal value 5–40 U/L) is usually meaningful.⁷ According to currently prevailing grading standards, liver damage can be divided into mild liver damage ($80 \text{ U/L} \leq \text{ALT} < 200 \text{ U/L}$), moderate liver damage ($200 \leq \text{ALT} < 600 \text{ U/L}$), and severe liver damage ($\text{ALT} \geq 600 \text{ U/L}$, typically with AST increased or the AST/ALT ratio increased).⁸

Assessment of etiology

Blood, urine, stool, and pharynx secretions were collected from patients. Blood culture, sputum culture, and urine culture were used for bacterial detection and identification. Viruses including cytomegalovirus, Epstein–Barr virus (EBV), enteroviruses (Coxsackie virus, Eck virus, rotavirus, and EV71), herpes simplex virus, respiratory syncytial virus, adenovirus, and hepatitis A/B/C/D/E viruses were detected using serological, antibody or PCR tests. *Mycoplasma pneumoniae* was detected used a combination of antigen and antibody tests. We also carried out chromosomal and genetic tests and used mass spectrometry of blood and urine to assess genetic metabolic diseases.

Etiology classification

Clinical data were classified according to the actual cause of liver damage. We excluded neonatal liver damage caused by perinatal diseases such as premature birth, neonatal asphyxia, and fetal distress. We excluded repeatedly diagnosed cases. Cases of multiple visits or hospital admissions for the same disease were counted as one case. In patients with a detailed diagnosis of

primary disease combined with liver damage, the etiology was recorded as the primary disease. For comprehensive evaluation of overlapping causes of liver damage, the most serious cause of liver damage was included in the disease spectrum to facilitate the analysis.

Results

Epidemiology of liver damage among children in Weifang

A total of 2632 patients with pediatric liver damage were identified, including 1572 boys and 1060 girls. Among these, 2100 patients (79.79%) had infectious liver damage, 446 patients (16.94%) had non-infectious liver damage, and in 86 patients the cause of liver damage could not be determined (3.27%). In the vast majority of patients, liver damage was mild or moderate (2601, 98.82%). There were 31 cases of severe liver damage (1.18%). The prevalence of liver damage among infants younger than 1 year was high (869/2632, 33.02%). There were 1026 cases of liver damage among preschool children aged 1 to 6 years (1026/2632, 38.98%). There were 737 cases of liver damage among school-age children aged 7 to 12 years (737/2632, 28.00%). See Table 1 and Table 2 for details.

Disease spectrum of liver damage in children

There were many causes of liver damage, and the causes were often complex. The most common causes of liver damage were infectious. The most common causes of infectious liver damage were viral infection (1515/2100, 72.14%), *Mycoplasma pneumoniae* infection (343/2100, 16.33%), and bacterial infections (197/2100, 9.38%). Other microbial infections, including infections by fungi and protozoa, may also cause

Table 1. Causes of liver damage in children in Weifang.

Cause of liver damage	Number of Cases (M/F)	Percentage (%)	Number of cases with severe liver damage
Infectious disease	2100 (1264/836)	79.79	2
Non-infectious disease	446 (249/197)	16.94	27
Unknown etiology	86 (49/37)	3.27	2
Total	2632 (1562/1070)	100	31

Table 2. Frequency of liver damage among children in Weifang by age.

Age group (years)	Number of cases	Percentage (%)	Number of cases with severe liver damage
< 1	869	33.02	9
1–6	1026	38.98	7
7–12	737	28.00	15
Total	2632	100	31

damage to the liver. The most common causes of viral liver damage were EBV (520/1515, 34.32%), cytomegalovirus (481/1515, 31.75%), and enterovirus (385/1515, 25.41%). Many types of non-infectious liver damage were observed with complex etiology. The most common causes of non-infectious liver damage were drug-induced liver damage (298/446, 66.82%), Kawasaki disease (37/446, 8.30%), and genetic metabolic liver damage (14/446, 3.14%). There were 86 cases of liver damage of unknown cause. See Table 3 and Table 4 for details.

Distribution of causes of liver damage by age

Liver damage in infants younger than 1 year was mainly associated with viral infection. In this age group, cytomegalovirus infection was the most common cause of liver damage (281/869, 32.34%), followed by enterovirus (176/869, 20.25%) and bacterial infection (114/869, 13.12%). The most common causes of liver damage among preschool age children aged 1 to 6

years were EBV infection (322/1026, 31.38%), cytomegalovirus infection (160/1026, 15.59%), and enterovirus infection (135/1026, 13.12%). There were 737 cases of liver damage among children aged 7 to 12 years. The most common causes of liver damage in this age group were *Mycoplasma pneumoniae* infection (247/737, 33.51%), EBV infection (156/737, 21.17%), and drug-induced liver damage (122/737, 16.5%). Viral infection was a common cause of liver damage in children of all ages. Among older children, the prevalence of drug-induced liver damage increased. See Table 5 for details.

Causes of severe liver damage

The causes of severe liver damage among children in Weifang were drug and toxic liver damage (n=11), autoimmune hepatitis (n=5), genetic metabolic diseases (n=4), biliary atresia (n=2), biliary obstruction (n=2), hepatopathy (n=2), congenital common bile duct (n=2), congenital choledochal cyst (n=1), EBV infection (n=1),

Table 3. Causes of infectious liver disease among children in Weifang (N=2100).

Viral hepatic damage		Non-viral hepatic damage	
Etiology of hepatic damage	Number of cases (M/F)	Etiology of hepatic damage	Number of cases (M/F)
Epstein–Barr virus	520 (301/219)	<i>Mycoplasma pneumoniae</i>	343 (215/128)
Cytomegalovirus	481 (294/187)	Bacterial infections	197 (109/88)
Enterovirus	385 (257/128)	Chlamydia	31 (14/17)
Influenza virus	43 (20/23)	Brucellosis	8 (5/3)
Respiratory syncytial virus	32 (18/14)	Whooping cough	4 (2/2)
Herpes virus	21 (9/12)	Fungal infections	1 (0/1)
Rubella virus	16 (9/7)	Qiang echinococcosis	1 (1/0)
Measles virus	4 (3/1)		
Adenovirus	3 (1/2)		
Hepatitis B virus	3 (2/1)		
Hepatitis C virus	1 (1/0)		
Others	6 (3/3)		
Total	1515 (918/597)	Total	585 (346/239)

bacterial infection (n=1), and unknown cause (n=2).

Discussion

The early diagnosis of liver damage mainly relies on serological testing of liver enzymes. Measurement of ALT levels is typically the simplest, most reliable, and most accurate marker of liver damage. ALT is an important enzyme in the body and can promote the conversion of proteins and amino acids in the cytoplasm of liver cells. ALT levels in the liver are 100 times those in the blood. Damage or necrosis of liver cells will increase the ALT levels in the blood. Therefore, ALT is the most sensitive indicator of liver damage and is used to aid diagnosis of liver disease and evaluation of liver damage.⁹

There are many causes of liver damage in children. Infection, drugs, hypoxia, anemia, autoimmunity, and other factors may cause liver damage. We studied the causes of liver damage among children aged ≤ 12 years in Weifang over a period of 10 years. We found that infections, and especially viral

infections, were the most common causes of liver damage, especially among younger children. This is consistent with the work of Shalimar et al.¹⁰ and with established patterns of childhood diseases. Among viral causes of liver damage, EBV and cytomegalovirus were the most common. The distributions of both viruses were age-related. Cytomegalovirus infectious liver damage was most common in infants under 1 year old, and EBV infection was more common after 1 year of age. The most common adult viral hepatitis was hepatitis B virus infection.¹¹ Because of the wide use of hepatitis B vaccines, the incidence of hepatitis B virus infection among children was very low.

EBV is a herpesvirus that mainly damages lymphocytes and is transmitted through saliva and blood.¹² EBV infection can cause multi-system organ damage. As an organ involved in immune defense, the liver can mobilize its cells to cooperate with lymphocytes in resisting virus-induced damage. Thus, liver damage is common following EBV infection.¹³ Children are more susceptible to EBV infection because of incomplete immune system development

Table 4. Causes of non-infectious liver disease among children in Weifang.

Non-infectious hepatic damage	
Etiology of hepatic damage	Number of cases (M/F)
Drug-induced hepatic damage	298 (171/127)
Kawasaki disease	37 (25/12)
Inherited metabolic disease	14 (8/6)
Autoimmune hepatitis	11 (4/7)
Juvenile idiopathic arthritis	3 (1/2)
Systemic vasculitis	2 (0/2)
Fatty liver	6 (4/2)
Epilepsy	5 (2/3)
Diabetes	4 (1/3)
Liver tumor	3 (2/1)
Langerhans cell tissue hyperplasia	3 (2/1)
Systemic lupus erythematosus	8 (1/7)
Hemolytic anemia	7 (4/3)
Allergic purpura	4 (1/3)
Biliary infection	6 (4/2)
Biliary obstruction	2 (2/0)
Biliary atresia	2 (1/1)
Congenital choledochal cyst	1 (1/0)
Blood disease	3 (2/1)
Rhabdomyolysis	2 (2/0)
Hepatolenticular degeneration	2 (1/1)
Hyperthyroidism	2 (1/1)
Progressive muscular dystrophy	3 (1/2)
Myasthenia gravis	2 (1/1)
Hemolytic uremic syndrome	1 (0/1)
Toadstool poisoning	8 (3/5)
Organophosphate poisoning	2 (1/1)
Drowning	3 (2/1)
Accidental trauma	2 (1/1)
Total	446 (249/197)

Table 5. Top three causes of liver damage among children in Weifang by age.

Age group (years)	Cause	Number of cases	Percentage (%)
< 1	Cytomegalovirus	281	32.34
	Enterovirus	176	20.25
	Bacterial	114	13.12
1–6	Epstein–Barr virus	322	31.38
	Cytomegalovirus	160	15.59
	Enterovirus	135	13.12
7–12	<i>Mycoplasma pneumoniae</i>	247	33.51
	Epstein–Barr virus	156	21.17
	Drug poisoning	122	16.55

before the age of 7 years. EBV infectious liver damage is more common in children younger than this age. Human cytomegalovirus infection is extremely widespread in China. Anti-cytomegalovirus antibodies can be detected in 86% to 96% of the general population and in about 95% of pregnant women.¹⁴ Most individuals have latent infections. When immunity is diminished in pregnant women, latent infections can become virulent and be transmitted to the newborn through milk. Therefore, cytomegalovirus is a common perinatal infection. The main clinical manifestations of cytomegalovirus infection are jaundice, hepatosplenomegaly, and liver damage.^{15,16} Viral liver damage may be related to direct damage to liver cells caused by the virus or to anti-viral immune responses.^{17,18} In recent years, the incidence of *Mycoplasma pneumoniae* infection has increased, leading to more frequent liver damage among preschool and school-age children.^{19,20} Kim et al.²¹ reported that the incidence of *Mycoplasma* infection among children with liver damage in South Korea was 7.7%. Chen et al.²² reported that the incidence of *Mycoplasma pneumoniae* infection in children with liver damage in Wenzhou was 10.26%. The potential for liver damage in children with *Mycoplasma pneumoniae* infection must be taken seriously in clinical practice.

Drug-induced liver damage was the most common non-infectious liver damage among children in our study, consistent with the results of Gan et al.²³ Antipyretic analgesics and antitumor drugs are the most common causes of drug-induced liver damage. Acetaminophen is the most used antipyretic and analgesic in children. It is widely used in China, the United States, the United Kingdom, and other countries,²⁴ and can cause severe drug-induced liver damage.²⁵ Patients with acute toxicity often show severe liver damage.²⁶ In recent years, traditional Chinese medicine

preparations have been widely used in children, and rates of drug-induced liver damage are also on the rise. There are currently more than 210 Chinese medicines that can cause liver damage.²⁷ Antibiotic-induced liver damage was relatively rare among children in Weifang. This finding differed from the conclusions drawn by Zheng et al.²⁸ in analyzing drug-induced liver damage among children across China from 2007 to 2016. This discrepancy may be related to differences in levels of medical care across different regions of China. The pathogenesis of drug-induced liver damage is complex and is incompletely understood. Typically, pathogenesis is summarized in terms of direct liver toxicity and idiosyncratic liver toxicity of drugs.^{29,30}

With the advancement of science and technology, diagnostic techniques continue to develop and novel types of inherited metabolic diseases are continuously discovered. This has expanded the spectrum of diseases associated with liver damage among children and increased the proportion of liver damage related to inherited metabolic diseases. Unexplained liver damage accounted for a large proportion of cases. This finding is related to deficiencies in current detection methods, incorrect results of pathogen detection tests, and insufficient understanding of liver damage. In addition, food pollution and environmental pollution can also cause liver damage in children. At present, there are no detection methods for these factors in our hospital. The appearance of fatty liver in children reflects changes in the spectrum of liver damage in children.^{31,32}

Severe liver damage in children is more commonly induced by drugs or poisons, especially muscarine, which is mostly ingested by eating wild poisonous mushrooms. Consumption of wild mushrooms should be discouraged to prevent poisoning. Dai et al.³³ showed that infectious diseases are the main causes of severe liver damage. This finding was inconsistent

with our study and may be related to the short study time and narrow scope.

In summary, this is was the first large-scale investigation of the causes of liver damage among children in Weifang. Although there were geographical limitations to our study, our data can be used to guide diagnostics and interventions in Shandong Province and China as a whole. Our results suggest that infections, especially viral infections, are the most common causes of liver damage among children. This finding is in line with the epidemiological characteristics of childhood diseases and is of clinical significance. We expect that with timely application of antiviral drugs and widespread vaccination, the incidence of infectious liver damage in children may be greatly reduced. As the global climate and living habits change, the spectrum of pediatric liver diseases is bound to change too. Unfortunately, we have not yet been able to conduct detailed research and analysis on changing trends of liver damage among children over time. In future studies, we hope to provide additional data to support a theoretical basis for early diagnosis and prevention of liver damage.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

Conception and design: Qinghong Meng and Xiaona Gao; administrative support: Qinghong Meng and Na Li; collection and assembly of data: Lianmei Yuan and Xiaona Gao; data analysis and interpretation: Na Li and Xiaona Gao. manuscript writing: all authors; and final approval of the manuscript: all authors.

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