The Diagnostic Value of Adenosine Deaminase in Children With Infectious Mononucleosis by EBV

Ting Shi

Soochow University Affiliated Children's Hospital

Jungen Li

Soochow University Affiliated No 1 People's Hospital: First Affiliated Hospital of Soochow University

Yuzhu Miao

Soochow University Affiliated No 1 People's Hospital: First Affiliated Hospital of Soochow University

Linlin Huang

Soochow University Affiliated Children's Hospital

Jianmei Tian (✉ 2231365607@qq.com)

Soochow University Affiliated Children's Hospital

Research

Keywords: Infectious mononucleosis, Adenosine deaminase, alanine aminotransferase

Posted Date: July 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-694945/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

Infectious mononucleosis (IM) which was a common disease in children was often accompanied by elevated transaminase and occasionally liver failure. This study aimed to explore the diagnostic value of adenosine deaminase in IM and its concurrent elevated alanine aminotransferase (ALT).

Methods

104 children with IM and 50 controls with acute infection, of whom main symptoms were fever, tonsillitis or lymphadenitis, from Children's Hospital of Soochow University were enrolled in this study. Among 104 children with IM, 54 had normal ALT (IM1 group) and 50 had elevated ALT (IM2 group). Then the clinical and laboratory data of the children were collected to explore the diagnostic value of ADA in the three groups.

Results

ADA in the IM group was significantly higher compared with it in the control group ($P < 0.001$). ADA had a high correlation with lymphocyte count, CD3 + CD8 + T cell (%), CD4+/CD8 + and CD3-CD19+(%) ($|r| > 0.7$, $p < 0.01$). ADA had great diagnostic value in pediatric patients with IM. The sensitivity and specificity of ADA in predicting pediatric IM patients were 97.1% and 94.0%, respectively. Furthermore, multivariate regression analysis indicated that ADA was risk factor for elevated ALT in children with IM.

Conclusions

ADA may be a novel diagnostic indicator for pediatric IM and indirectly predict elevated ALT.

Background

Infectious mononucleosis (IM) was an acute EBV infection and presents with a classical triad: fever, pharyngitis and lymphadenopathy [1]. It mostly occurred in pediatric, adolescent and young adult patients. In European and American countries, it mainly affected in adolescence and adults, mostly in 10–30 years old [2]. But in China, it usually occurs in children 4–6 years old [3]. Elevated transaminase is the most common complication of infectious mononucleosis. Numerous studies [4, 5, 6] have indicated that elevated transaminase was seen in up to 80–90% of patients, while jaundice was rare in primary EBV infection. Although such hepatitis is usually mild and can go undetected with spontaneous resolution, there are described cases with complications like severe hepatitis or acute hepatic failure [6, 7].

Adenosine deaminase (ADA) is a purine metabolism enzyme encoded by the ADA gene, of which the mutations can lead to severe combined immune deficiency (SCID) [8]. A large number of studies have confirmed that ADA played an important role in growth and differentiation of lymphocytes and macrophages, and it was considered as a marker of T lymphocyte-mediated cellular immunity [9]. Elevated ADA can be

observed in autoimmune diseases, acquired immune deficiency syndrome (AIDS) and tumors, and its level were closely related to the severity of these disease [10, 11]. Although the ADA is known to be associated with numerous diseases, its utility in pediatric patients with IM has remained elusive. The aim of the present study was to explore the diagnostic value of adenosine deaminase in children with infectious mononucleosis and its concurrent elevated ALT, which can provide clues to clinicians for timely diagnosis of IM and judgment of disease severity.

Materials And Methods

Patient characteristics

The present prospective study was performed at the Children's Hospital of Soochow University (Suzhou, China). 104 children with IM were enrolled in this study from July 2019 to December 2019, and courses of disease > 5 days, mixed infections, chronic diseases and autoimmune diseases were excluded. There were 47 males and 57 females, with median age of 2.9(1.9-4.1) years. Among them, 54 children had normal ALT (IM1 group) and 50 patients with elevated ALT (IM2 group). 50 patients with acute infection, of whom main symptoms were fever, tonsillitis, or lymphadenitis, in the same period served as control group (non-IM group), 27 males and 23 females, with median age of 3.2(2.2 ± 5.1) years. There was no difference in sex, age and courses of disease between the two groups ($p > 0.05$), which was comparable. The inclusion criteria of the control group were courses of disease < 5 days, EBV-specific antibodies test was negative and no history of immune system diseases, chronic infectious diseases and immunomodulator used in the past two weeks. The present study was approved by the medical ethics committee of the Children's Hospital of Soochow University (protocol numbers:2019KS004) and it conforms to provisions of the Declaration of Helsinki. the criteria for IM as follows[12]: (1) presence of at least three of the following clinical manifestations: fever, tonsillopharyngitis, cervical lymphadenopathy, hepatomegaly or splenomegaly; (2) IgM to EBV viral capsid antigen (VCA-IgM) and IgG to EBV capsid antigen (VCA-IgG) were positive, with absence of an antibody to Epstein-Barr nuclear antigen (EBNA); VCA-IgM negative, but VCA-IgG antibody positive which was low affinity antibody(Euroimmun Medical Diagnosis Co., Ltd, Lubeck, Germany); (3) The viral infections such as cytomegalovirus (CMV), human immunodeficiency virus (HIV), herpes simplex virus (HSV) and hepatotropic virus were excluded. Upon patient admission to the hospital, their pediatricians completed a questionnaire regarding the patient demographic and clinical data. peripheral blood samples were obtained for detection.

biochemical and lymphocyte subsets examination

peripheral blood samples were obtained for detection within 24 hours of admission. Routine complete blood count (CBC) of peripheral blood from participants was performed using the type BC-5310 instrument (Shenzhen Mindray Biomedical Electronics Co., Ltd), quantitative determination of adenosine deaminase activity in serum used peroxidase method (Meikang Biotechnology Co., Ltd), biochemical parameters were detected on a HITACHI 7180 biomedical analyzer, and flow cytometry Epics XL-MCL (Backman Coulter) was used to detect lymphocyte subsets. All reagents for testing were the original reagents of the instruments.

EBV specific antibodies test

Specific antibodies to EBV were detected using an indirect immunofluorescence (IIF) assay. Venous blood sample (2 mL) was collected and centrifuged, then serum was obtained for subsequent experiments. Serum viral capsid antigen (VCA)-IgM, VCA-IgG, early antigen (EA)-IgG, nuclear antigen (EBNA)-IgG antibodies specific to EBV were tested using the EBV kit IFA (EUROIMMUN, Lübeck, Germany) following the manufacturer's instructions. The affinity of VCA-IgG was determined by comparing the fluorescence intensity using the serum from children treated with and without urea: <2 levels=high-affinity and ≥ 2 levels=low-affinity.

Statistical Analysis

The Shapiro-Wilk normality test was used to determine if the data is normally distributed. Values were expressed as the mean $\pm$ standard deviation or median (interquartile range). The Mann-Whitney U test and Kruskal-Wallis test were used for skewed distributed data and Student's t-test for normal distribution variables. Categorical variables were presented as n (%) and analyzed with the Chi-squared test or Fisher's exact test. Spearman correlation analysis was used for discrete variable data. Logistic regression analysis was used to determine odds ratios (OR) with 95% CI. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy of adenosine deaminase in children with infectious mononucleosis. All statistical analyses were performed using SPSS version 25.0 (IBM Corp.). $P < 0.05$ was considered to indicate statistical significance.

Results

Clinical characteristics of IM group and Control group

A total of 104 cases with IM and 50 control children with acute infectious disease were enrolled in the present study. As shown in Table 1, the amounts of lymphocyte count, ADA, IgA, IgG, IgM, CD3+ (%) and CD3 + CD8+ (%) in children with IM were all significantly increased compared with controls ($P < 0.001$). However, the value of CD3 + CD4+ (%), CD4+/CD8+, CD3-CD19+ (%) and CD19 + CD23+ (%) were lower in the IM group ($P < 0.001$).

Table 1
Comparison of Laboratory Findings between IM group and non-IM group

Parameters	IM group (n = 104)	Non-IM group (n = 50)	P
Gender(male)	47(45.2)	27(54.0)	0.306
Age	2.9(1.9–4.1)	3.2(2.2–5.1)	0.207
Disease course	3.0(3.0–4.0)	3.0(2.8-4.0)	0.263
WBC ($\cdot 10^9/L$)	16.4(12.3–21.0)	13.7(9.3–19.3)	0.049
Lymphocyte count($\cdot 10^9/L$)	10.6(7.0–14.0)	3.4(2.3–5.2)	< 0.001
ADA(U/L)	51.6(44.5–66.5)	20.1(17.1–23.8)	< 0.001
IgA(g/L)	1.4(1.0-1.9)	0,8(0.5–1.2)	< 0.001
IgG(g/L)	11.3 $\pm$ 2.8	7.7 $\pm$ 2.2	< 0.001
IgM(g/L)	1.6(1.3–2.2)	1.1(0.8–1.6)	< 0.001
CD3+ (%)	79.1(72.6–82.8)	63.8(54.1–71.8)	< 0.001
CD3 + CD4+ (%)	17.6(13.3–21.7)	32.1(24.8–39.2)	< 0.001
CD3 + CD8+ (%)	53.9 $\pm$ 11.0	25.0 $\pm$ 8.0	< 0.001
CD4+/CD8+	0.3(0.2-0.475)	1.2(1.0-1.7)	< 0.001
CD3-CD(16 + 56)+(%)	11.9(8.1–16.9)	11.1(6.7–16.1)	0.616
CD3-CD19+ (%)	7.8(5.2–9.8)	20.9(16.0-29.8)	< 0.001
CD19 + CD23+ (%)	4.0(2.4–6.3)	9.9(6.8–12.7)	< 0.001
Notes: The data presented as median [interquartile range], mean $\pm$ standard deviation and n (%). The univariate analyses were performed using Mann-Whitney U-test for skewed distribution variables, t-test for normal distribution variables and the chi-square test for categorical variables. Abbreviation: WBC: white blood cell, ADA: adenosine deaminase, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM, immunoglobulin M.			

Correlation Of Ada With Laboratory Parameters

As shown in Fig. 1, ADA had a high correlation with lymphocyte count, CD3 + CD8 + T cell (%), CD4+/CD8 + and CD3-CD19+(%) ($|r| > 0.7$, $p < 0.01$). Lymphocyte count and CD3 + CD8 + T cell (%) were positively correlated with ADA, while CD4+/CD8 + and CD3-CD19+ (%) were negatively correlated with ADA.

Diagnostic Accuracy Of Ada In Im

As shown in Fig. 2, ADA had a great diagnostic value for IM. The cut-off value for ADA was set at 32.14U/L, the sensitivity was 97.1%, the specificity was 94.0% with an area under the curve calculated to be 0.987($P < 0.05$).

Predictive Value Of Ada For Alt In Im Patients

As shown in Table 2, There is no statistical difference in clinical manifestations between IM patients with elevated (IM2 group) and normal ALT (IM1 group) ($P > 0.05$). The amounts of lymphocyte count, plasma DNA load, ADA, IgG, IgM, CD4+, CD3 + CD8+, CD4+/CD8 + and CD3-CD19 + were statistically different between IM1group and IM2 group (Table 3). As shown in Table 4, univariate and multivariate logistic regression analysis found ADA was an independent risk factor for elevated ALT (aOR = 1.126, 95% CI 1.063–1.192). ROC curve analysis was used to evaluate the diagnostic value of ADA for ALT (Fig. 2). The sensitivity and specificity are 92.0% and 79.6%, respectively. ADA had good value in diagnosing IM (cut-off value, 32.14U/L) and predicting elevated ALT (cut-off value, 50.13 U/L) (Fig. 3).

Table 2
Clinical Characteristics of IM patients with normal and elevated ALT

Parameters	IM1 group (n = 54)	IM2 group (n = 50)	<i>P</i>
Gender(male)	23(42.6)	24(48.0)	0.580
Age	3.2(1.9–4.4)	2.8(2.0–4.0)	0.519
Disease course	3.0(3.0–4.0)	4.0(3.0–4.0)	0.113
Peak of fever (°C)	39.2(38.7–39.5)	39.1(38.9–39.5)	0.688
Tonsillar white coat	47(87.0)	41(82.0)	0.477
Cervical lymphadenopathy	54(100.0)	49(98.0)	0.481
Hepatomegaly	15(27.8)	16(32.0)	0.638
Splenomegaly	18(33.3)	21(42.0)	0.362
Rash	9(16.7)	7(14.0)	0.706
Puffy eyelid	39(72.2)	34(68.0)	0.638
Notes: The data are reported as median (interquartile range) or n (%). The univariate analyses were performed using Mann-Whitney U test for skewed distributed data and the chi-square test or fisher's exact test for categorical variables. IM1 group represents the normal ALT group, IM2 group represents elevated ALT group.			

Table 3
Laboratory Findings of IM patients with normal and elevated ALT

Parameters	IM1 group (n = 54)	IM2 group (n = 50)	<i>P</i>
WBC ($\cdot 10^9/L$)	15.3(11.4–19.5)	17.2(12.8–23.3)	0.08
Lymphocyte count($\cdot 10^9/L$)	10.4(6.4–12.7)	11.8(7.4–16.1)	0.042
Plasma EBV-DNA Ig(copies/ml)	3.7 $\pm$ 0.6	4.1 $\pm$ 0.7	0.003
ADA(U/L)	45.1(38.9–49.4)	62.3(53.4–79.3)	< 0.01
IgA(g/L)	1.4 $\pm$ 0.6	1.6 $\pm$ 0.7	0.110
IgG(g/L)	10.4 $\pm$ 2.5	12.2 $\pm$ 2.8	0.001
IgM(g/L)	1.4(1.1-2.0)	1.8(1.4–2.2)	0.022
CD3+ (%)	78.1(71.0-82.8)	79.4(75.0-82.7)	0.342
CD3 + CD4+ (%)	19.1(14.5–23.3)	15.6(12.6–20.6)	0.008
CD3 + CD8+ (%)	51.6 $\pm$ 10.1	56.3 $\pm$ 11.4	0.027
CD4+/CD8+	0.4(0.3–0.5)	0.3(0.2–0.4)	0.006
CD3-CD(16 + 56)+(%)	12.2 $\pm$ 5.7	12.6 $\pm$ 5.7	0.730
CD3-CD19+ (%)	9.0 $\pm$ 4.8	7.1 $\pm$ 3.2	0.021
CD19 + CD23+ (%)	4.4(2.4–6.4)	3.5(2.4–6.1)	0.499
Notes: The data presented as median [interquartile range], mean $\pm$ standard deviation and n (%). The univariate analyses were performed using Mann-Whitney U-test for skewed distribution variables, t-test for normal distribution variables. IM1 group represents the normal ALT group, IM2 group represents elevated ALT group. Abbreviation: WBC: white blood cell, ADA: adenosine deaminase, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM, immunoglobulin M.			

Table 4
Factors associated with elevated ALT in IM patients (multivariate analysis)

Variable	Model 1		Model 2		Model 3	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
Lymphocyte($\cdot 10^9/L$)	1.066(0.995–1.141)	0.068	1.066(0.994–1.144)	0.075		
Plasma EBV-DNA Ig(copies/ml)	2.551(1.325–4.912)	0.005	2.650(1.358–5.173)	0.004	1.311(0.645–2.663)	0.454
ADA(U/L)	1.125(1.073–1.179)	< 0.01	1.129(1.075–1.185)	< 0.001	1.126(1.063–1.192)	< 0.001
IgG(g/L)	1.297(1.103–1.525)	0.002	1.349(1.130–1.610)	0.001	1.057(0.827–1.350)	0.658
IgM(g/L)	2.089(1.134–3.848)	0.018	2.188(1.182–4.048)	0.013	1.479(0.581–3.763)	0.412
CD4+ (%)	0.962(0.909–1.018)	0.184	0.957(0.901–1.018)	0.161		
CD8+ (%)	1.042(1.004–1.082)	0.030	1.050(1.008–1.093)	0.019	0.955(0.880–1.037)	0.955
CD4+/CD8+	0.031(0.002–0.376)	0.006	0.017(0.001–0.278)	0.004	0.144(0.001–37.818)	0.496
CD3-CD19+ (%)	0.890(0.804–0.986)	0.026	0.878(0.790–0.976)	0.016	1.042(0.892–1.217)	0.605
Abbreviations: ALT: alanine aminotransferase, IM: infectious Mononucleosis, ADA: adenosine deaminase, IgG: immunoglobulin G, IgM: immunoglobulin M, OR: odds ratio, CI: confidence interval. Model 1 was not adjusted. Model 2 was adjusted for age and gender. Model 3 was adjusted as Model 2 + Plasma EBV-DNA, ADA, IgG, IgM, CD8+ (%), CD4+/CD8+, CD3-CD19+ (%).						

Discussion

Epstein-Barr virus (EBV) is a globally prevalent herpesvirus. The symptoms of EBV infection in children are often atypical [13], and the diagnosis mainly relies on serological assay [14]. Clinically, the patient's biochemical test result was earlier than the EBV-specific antibodies test. In this study, ADA in children with IM was significantly higher than the acute infectious diseases caused by other pathogens, and it has a good diagnostic value for IM. And when IM is accompanied by elevated ALT, ADA also has a great predictive value, which can indirectly reflect the severity of the disease. So, ADA can help clinicians to diagnose IM early.

Infectious mononucleosis (IM) was an acute EBV infection and presents with a classical triad: fever, pharyngitis and lymphadenopathy [1], which were difficult to distinguish from febrile diseases caused by other pathogens. Previous studies [15, 16] have confirmed that lymphocytes were significantly elevated in children with IM, especially CD8 + T cells, and CD4/CD8 inversion occurs. That was consistent with this study. In addition, this study found that immunoglobulins (IgA, IgG and IgM) in children with IM were higher than

infectious diseases caused by other pathogens. This suggested that humoral immunity also plays an important role in IM caused by EBV infection.

This study also found that ADA was significantly increased in children with IM, and there was a high correlation with lymphocytes. Previous studies [9] have shown that ADA played an important role in growth and differentiation of lymphocytes and macrophages. In summary, it is suggested that ADA plays a certain role in IM, which provided clues for further research in the future. Through ROC curve analysis, it was showed that ADA had a good diagnostic value for IM caused by EBV in acute febrile diseases. The most common complication of infectious mononucleosis was elevated transaminases [4, 5, 6]. In this study, there was no difference in clinical manifestations between children with elevated and normal ALT. Through the comparison of laboratory indicators, the lymphocyte, viral load, ADA, CD8 + Tcell (%), IgG and IgM were higher in the children with elevated ALT. The previous study reported that lymphocytosis was a feature of Epstein-Barr virus-related liver damage [17]. Some studies have shown that EBV-NDA copy number was directly proportional to the severity of infectious mononucleosis [18], but it had no correlation with the pathogenesis of EBV-related liver damage. Although the mechanism of EBV hepatitis is still unclear, views supported by current research that EBV infected and activated CD8 + T cells may accumulate in the liver and the products of the EBV-infected CD8 + T cells or infiltrating cytotoxic T lymphocytes were interferon- γ , tumor necrosis factor and Fas ligand, which can destroy hepatocytes [19, 20, 21, 22]. In this study, multivariate regression analysis shows that only ADA was an independent influencing factor of ALT. Combined with ROC curve analysis, ADA had a good predictive value for ALT in IM. The previous research has shown that ADA level can predict severity of disease in hepatitis B, C and autoimmune hepatitis [23], But there was no report about its predictive effect of IM combined with elevated transaminase. According to the above statement, whether ADA is involved in the mechanism of infectious mononucleosis complicated by liver damage is worthy of our consideration.

Our study has several limitations. First, since most of the IM-complicated transaminase is self-limiting, liver biopsy is lacking. If the correlation between ADA and liver cell injury can be explored, more reliable results can be obtained. Secondly, this study lacks dynamic monitoring of the correlation between ADA and ALT.

Conclusion

ADA had a good diagnostic value for IM in children with acute febrile diseases. ADA was highly correlated with lymphocytes in children with IM, especially CD8 + T cells. In addition, it has a certain predictive effect on IM combined with elevated ALT. This can help clinicians diagnose IM early and predict the severity of the disease.

Abbreviations

IM

Infectious mononucleosis; ALT:alanine aminotransferase; OR:odds ratio; CI:confidence interval; ROC:Receiver operating characteristic; WBC:white blood cell; ADA:adenosine deaminase; IgA:immunoglobulin A; IgG:immunoglobulin G; IgM, immunoglobulin M; ADA:adenosine deaminase.

Declarations

Acknowledgements

The authors wish to thank laboratory of children's Hospital of Soochow University that provided the data for EBV serological and biochemical test analysis.

Author contributions

Acquisition of data: Ting Shi, Linlin Huang and Jungen Li. Analysis and interpretation of data: Ting Shi, Linlin Huang, Jungen Li. Drafting the article: Ting Shi, Linlin Huang, Yuzhu Miao. Revising critically the manuscript for important intellectual content: Jianmei Tian, Ting Shi, Linlin Huang. All authors approved the final version of the manuscript submitted.

Funding

The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request (2231365607@qq.com; shiting0915@126.com).

Ethics approval and consent to participate

This study was conducted with the approval of the Institutional Human Ethical Committee of Children's Hospital of Soochow University. An informed consent was obtained from all the subjects or guardians who participated in this study.

Consent for publication

All authors have read and approved the content, and they agree to submit it for consideration for publication in the journal.

Competing interests

The authors declare that they have no competing interests

References

1. Luzuriaga K, Sullivan JL. Infectious mononucleosis. *N Engl J Med*. 2010;362(21):1993–2000.
2. Dowd JB, Palermo T, Brite J, McDade TW, Aiello A. Seroprevalence of Epstein-Barr virus infection in U.S. children ages 6–19, 2003–2010. *PLoS One*. 2013;8(5):e64921.
3. Gao LW, Xie ZD, Liu YY, Wang Y, Shen KL. Epidemiologic and clinical characteristics of infectious mononucleosis associated with Epstein-Barr virus infection in children in Beijing, China. *World J Pediatr*. 2011;7(1):45–9.

4. Yang SI, Geong JH, Kim JY. Clinical characteristics of primary Epstein Barr virus hepatitis with elevation of alkaline phosphatase and γ -glutamyltransferase in children. *Yonsei Med J*. 2014;55(1):107–12.
5. Crum NF. Epstein Barr virus hepatitis: case series and review. *South Med J*. 2006;99(5):544–7.
6. Shaw NJ, Evans JH. Liver failure and Epstein-Barr virus infection. *Arch Dis Child*. 1988;63(4):432–3.
7. Mellinger JL, Rossaro L, Naugler WE, et al. Epstein-Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. *Dig Dis Sci*. 2014;59(7):1630–7.
8. Bradford KL, Moretti FA, Carbonaro-Sarracino DA, Gaspar HB, Kohn DB. Adenosine Deaminase (ADA)-Deficient Severe Combined Immune Deficiency (SCID): Molecular Pathogenesis and Clinical Manifestations. *J Clin Immunol*. 2017;37(7):626–37.
9. Antonioli L, Colucci R, La Motta C, et al. Adenosine deaminase in the modulation of immune system and its potential as a novel target for treatment of inflammatory disorders. *Curr Drug Targets*. 2012;13(6):842–62.
10. Ghaderi B, Amini S, Maroofi F, et al. Adenosine Deaminase Activity in Chronic Lymphocytic Leukemia and Healthy Subjects. *Iran J Cancer Prev*. 2016;9(3):e5069.
11. Naval-Macabuhay I, Casanova V, Navarro G, et al. Adenosine deaminase regulates Treg expression in autologous T cell-dendritic cell cocultures from patients infected with HIV-1. *J Leukoc Biol*. 2016;99(2):349–59.
12. Kaya S, Cetin ES, Aridogan BC, Arikan S, Demirci M. Adenosine deaminase activity in serum of patients with hepatitis – a useful tool in monitoring clinical status. *J Microbiol Immunol Infect*. 2007;40(4):288–92.
13. Winter JR, Taylor GS, Thomas OG, Jackson C, Lewis J, Stagg HR. Predictors of Epstein-Barr virus serostatus in young people in England. *BMC Infect Dis*. 2019;19(1):1007.
14. AbuSalah M, Gan SH, Al-Hatamleh M, Irekeola AA, Shueb RH, Yean Yean C. Recent Advances in Diagnostic Approaches for Epstein-Barr Virus. *Pathogens*. 2020. 9(3).
15. Barros M, Vera-Lozada G, Segges P, Hassan R, Niedobitek G. Revisiting the Tissue Microenvironment of Infectious Mononucleosis: Identification of EBV Infection in T Cells and Deep Characterization of Immune Profiles. *Front Immunol*. 2019;10:146.
16. Lam J, Hui KF, Ning RJ, Xu XQ, Chan KH, Chiang A. Emergence of CD4 + and CD8 + Polyfunctional T Cell Responses Against Immunodominant Lytic and Latent EBV Antigens in Children With Primary EBV Infection. *Front Microbiol*. 2018;9:416.
17. Vine LJ, Shepherd K, Hunter JG, et al. Characteristics of Epstein-Barr virus hepatitis among patients with jaundice or acute hepatitis. *Aliment Pharmacol Ther*. 2012;36(1):16–21.
18. Kimura H, Kwong YL. EBV Viral Loads in Diagnosis, Monitoring, and Response Assessment. *Front Oncol*. 2019;9:62.
19. Kimura H, Nagasaka T, Hoshino Y, et al. Severe hepatitis caused by Epstein-Barr virus without infection of hepatocytes. *Hum Pathol*. 2001;32(7):757–62.
20. Shi J, Ma W, Li W. Epidemiologic features of children with Epstein-Barr virus associated diseases in Hangzhou, China. *J Med Virol*. 2020;92(8):1277–82.

21. Bradham CA, Plümpe J, Manns MP, Brenner DA, Trautwein C. Mechanisms of hepatic toxicity. I. TNF-induced liver injury. *Am J Physiol*. 1998;275(3):G387-92.

22. Kondo T, Suda T, Fukuyama H, Adachi M, Nagata S. Essential roles of the Fas ligand in the development of hepatitis. *Nat Med*. 1997;3(4):409–13.

23. Kaya S, Cetin ES, Aridogan BC, Arikan S, Demirci M. Adenosine deaminase activity in serum of patients with hepatitis – a useful tool in monitoring clinical status. *J Microbiol Immunol Infect*. 2007;40(4):288–92.

Figures

Figure 1 Correlation between adenosine deaminase and immune cells/globulin

Figure 1

See image above for figure legend

Figure 2 The diagnostic value of adenosine deaminase in infectious mononucleosis. (A) The diagnostic value of adenosine deaminase for IM. (B) the diagnostic value of adenosine deaminase for IM with elevated alanine aminotransferase.

Figure 2

See image above for figure legend

Figure 3 The level (Interquartile range) of adenosine deaminase in the non-IM group, IM1 group (IM with normal ALT) and IM2 group (IM with elevated ALT) . Threshold(A) for diagnosing IM and threshold(B) for diagnosing IM with elevated ALT. IM, Infectious Mononucleosis; ALT, Alanine aminotransferase; *, $p < 0.05$.

Figure 3

See image above for figure legend