The utility of liver function tests and abdominal ultrasound in infectious mononucleosis – A systematic review

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Abstract

Introduction: A large proportion of patients with infectious mononucleosis (IM) have abnormal liver function tests (LFT) at presentation. There is no guideline regarding the management and follow-up of these patients. Some patients also have abdominal ultrasound due to deranged LFT, the need for this practice is unclear. The aim of this systematic review was to evaluate the evidence base on LFT assessment in IM, time to resolution of derangement, and the role of abdominal ultrasound. Methods: A systematic search of PubMed, EMBASE and the Cochrane library was done. Two authors independently screened records for eligibility using pre-defined criteria. We included both adult and paediatric populations. Quality assessment of included studies was done. Results: A total of 3924 patients were included from 32 studies. A combination of typical clinical features, heterophile antibodies and EBV-specific antibodies were used to ascertain diagnosis. The following proportion of patients had abnormal LFTs: AST (57%); ALT (62%); ALP (65%); Bilirubin (16%); GGT (41%). Reported median (i.q.r.) time to resolution of LFT was 8 (6–12) weeks. Maximum time to resolution was >6 months. Clinical hepatomegaly and splenomegaly were found in 35% and 44% of patients respectively. Enlarged liver and spleen on ultrasound were seen in 16/29 (55%) and 38/38 (100%) of patients respectively. There were no reports of decompensated liver disease. Conclusion: Derangement in LFTs can persist over six months from initial presentation in IM. However, this is self-limiting. The evidence suggests serial liver function assessments and ultrasound abdomen are not required in immunocompetent patients with subclinical derangement in LFTs.

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had abnormal LFTs: AST (57%); ALT (62%); ALP (65%); Bilirubin (16%); GGT (41%). Reported median (i.q.r.) time to resolution of LFT was 8 (6–12) weeks. Maximum time to resolution was >6 months. Clinical hepatomegaly and splenomegaly were found in 35% and 44% of patients respectively. Enlarged liver and spleen on ultrasound were seen in 16/29 (55%) and 38/38 (100%) of patients respectively. There were no reports of decompensated liver disease.

Conclusion

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Word count: 250 words

Keywords: Infectious mononucleosis; glandular fever; liver function; abdomen ultrasound; Epstein-Barr virus

5 succinct key points

- Derangement in liver enzymes is common in patients with infectious mononucleosis.
- The reported median time to resolution of deranged liver function tests is 8 weeks but can persist beyond six months in a minority of patients.
- Deranged LFTs caused by infectious mononucleosis is self-limiting in majority of patients.
- Evidence suggests serial blood tests until resolution is not required in immunocompetent patients with subclinical derangement in LFTs.
- Routine abdominal ultrasound is not required in IM to investigate deranged liver function test in immunocompetent patients with subclinical derangement in LFTs.

Introduction

Infectious mononucleosis (IM) is a relatively common presentation to the Ear, Nose and Throat (ENT) department, with patients being admitted for symptomatic relief and hydration. These are generally young patients without medical comorbidities. The Epstein-Barr virus (EBV) is the most common cause of IM, with the remainder due to other viruses including cytomegalovirus (CMV), toxoplasmosis, and HIV.[1]

In patients with clinically suspected IM and atypical lymphocytosis, the diagnosis is generally confirmed with the monospot test. However, there is a false negative rate in up to 25% of adults in the first week of symptoms.[2]

There is abnormality in liver function tests (LFT) in a large proportion of patients presenting with IM but this is usually self-limiting.[2] Patient admitted to hospital generally would have standard LFTs as part of initial work up for IM. The utility of this is unclear, however, it may support diagnosis in the first week of illness if the monospot test was falsely negative. In addition, in settings where there is no available screening or definitive tests for IM, deranged LFTs may support clinical diagnosis taken in conjunction with clinical symptoms.

Practice varies with regards to follow-up in patients with IM and abnormal LFTs. Although a self-limiting finding, an initially abnormal LFTs generally start a cascade for further tests until normal. Anecdotally, general practitioners are often asked to repeat LFTs at varying intervals following discharge from hospital to ensure resolution. There are no guidelines to inform this practice. In addition, some centres routinely do abdominal ultrasound to evaluate the liver and spleen in patients with IM and abnormal LFTs; the need for this practice is unclear.

This systematic review aims to evaluate evidence base on LFTs assessment and ultrasound abdomen in IM. Specifically, we sought to determine the proportion of patients with abnormal LFTs, time to resolution of abnormal LFTs from clinical presentation, findings on abdominal ultrasound, and occurrence of decompensated liver disease.

Methods

A systematic search of PubMed, EMBASE and Cochrane library was done with no restriction on publication date. The following search strategy was used: [infectious mononucleosis OR glandular fever] AND [liver function* OR liver enzyme* OR ultrasound]. Two authors (ETT, DW) independently screened title and abstract according to prespecified criteria and full texts of relevant articles were retrieved for further eligibility assessment. References of included full text articles were further screened for relevant studies. Any discrepancies on study eligibility were discussed with a third author (OE) and resolved accordingly.

We included all original studies evaluating any form of LFTs and/or abdominal ultrasound (USS) in both adult and/or paediatric patients with suspected or confirmed diagnosis of IM. Standard LFTs included any of the following: Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Bilirubin, Albumin, Total protein and Gamma-Glutamyltransferase (GGT). Abdominal ultrasound included liver and/or spleen and/or gallbladder ultrasound. We excluded studies evaluating patients with solely viral hepatitis (i.e. not related to clinical presentation of infectious mononucleosis), reviews, non-human studies, conference abstracts, letters/commentaries, expert opinions or recommendations, case reports and studies not published in English.

A standardized data collection proforma was used. This was initially piloted on five studies by all authors and revised accordingly. Subsequent data collection was by one author (DW) and checked for accuracy by a second author (ETT). In case of duplicate publications, we included the manuscript with the most complete data. The following data items were extracted: study characteristics, participants' demographics, method of ascertainment of IM, evaluation of LFTs, clinical findings on abdominal ultrasound and complications relating to liver disease. Our main outcomes are the proportion of patients with abnormal LFTs at presentation and time to resolution of LFTs. Secondary outcomes include presence of clinical hepatosplenomegaly, findings of abdominal ultrasound and any evidence of decompensated liver disease.

Quality assessment of included studies were performed using Murad's tool.[3]Although the tool was originally developed for case series and case reports, this was discussed among the authors and deemed suitable for our review irrespective of study type as we were only extracting data relating to a single arm of interest. Data was expressed as count and percentages. Proportion of abnormal LFTs in individual studies were aggregated and an average calculated for all studies.

PRISMA reporting guideline was used in preparation of the manuscript.

Results

Figure 1 shows the PRISMA flow diagram for selection of studies. A total of 32 studies were included; one multicentered randomized controlled trial, seven case-control studies and the remaining were observational studies. Results of the quality assessment of included articles are shown in Table 1. The studies included a total number of 3,924 patients. Five studies evaluated only adult population[4-8]; ten studies were on paediatric population (defined as under 18 years)[9-18]; ten studies included both adult and children[19-28]; eight studies did not report on the participants' age [29-36].

Diagnosis of infectious mononucleosis

Table 2 shows the different methods used to ascertain IM. Sixteen studies evaluated IM specifically caused by EBV using EBV-specific antibodies such as IgM and/or IgG with absence of EBNA while one study only evaluated CMV mononucleosis confirmed by CMV IgM[6] and PCR. Thirteen studies used a combination of typical clinical symptoms (fatigue, fever, sore throat and swollen lymph nodes), presence of heterophile antibodies, and lymphocytosis or atypical lymphocytes to diagnose IM. Two studies did not report on method of diagnosis of IM [30,19].

Main outcomes

We evaluated the proportion of patients with IM who had elevated LFTs in individual studies (Table 3). At presentation the following proportion of patients had elevated parameters: AST, 835/1472 (56.7%);

ALT, 957/1546 (61.9%); ALP, 271/417 (65.0%); Bilirubin, 188/1160 (16.2%); GGT, 258/626 (41.2%). Six studies did not differentiate between the transaminases and reported 435/891 (48.8%) patients with raised values. Zhang et al. found reduce levels of total bilirubin in patients with IM compared to healthy control. Two studies included albumin within their testing and reported reduced albumin levels in 21/114 (18.4%) patients[27,35].

Data on resolution of abnormal LFTs was largely incompletely reported (Table 3). Eleven studies reported following up patients with abnormal LFTs. Of these, eight studies reported maximum time to resolution of LFTs. The reported median (i.q.r.) time to complete resolution of all liver function parameters was 8 (6 – 12) weeks. One study found persistently raised LFTs in a small number of patients after 6 months of presentation [26].

Secondary outcomes

Eighteen studies reported on clinical findings of hepatomegaly;1039/2967 (35.0%) patients were considered to have enlarged livers on clinical palpation. Twenty-one studies reported on clinical findings of splenomegaly,1311/3009 (43.6%) patients were found to have enlarged palpable spleens on clinical examination.

Three studies reported on abdominal ultrasound findings in patients with IM [4,11,24]. In a case-control study, Ishibashi et al. found that all nine IM patients had significantly enlarged spleen on ultrasound. However, only three (33.3%) had splenomegaly on clinical examination. Another study found that all 29 patients with IM had enlarged spleen on ultrasound and 16 (55.2%) had enlarged liver[24]. Clinical findings of splenomegaly and hepatomegaly were 17.2% and 10.3% respectively in that study.

Mazur et al performed USS gallbladder on all IM patients and found 15/181 (8.3%) of children had acute acalculous cholecystitis (AAC). The cohort with AAC reported right upper quadrant pain in addition to the typical clinical symptoms of IM. None required surgical intervention.

No additional interventions were reported in patients who had elevated bilirubin or clinical jaundice. There were no reports of decompensated acute or chronic liver disease among studies that followed patients for complications relating to IM.

Discussion

To our knowledge, this is the first systematic review to evaluate LFTs and USS in IM. Abnormal LFTs are an expected feature in IM; many units will routinely do blood tests to assess liver function on admission. The NICE clinical knowledge summary mentioned clinicians should consider blood test for LFTs in IM; based on expert opinion.[37]The utility of this practice is unclear.

Our systematic review found around two thirds of patients had elevated transaminases; this is lower than other reports of 80-90%[2]. This difference may be attributed to timing of LFT measurements and the heterogenous population of the systematic review. It is commonly accepted that time to resolution of abnormal LFTs from presentation with IM is around three to four weeks [38]. However, the median reported time to resolution was eight weeks; a small minority of patients had persistent derangement after 6 months.

The population affected with IM are generally young and healthy. Evidence from the literature suggest serial measures of LFTs following discharge is not necessary, given the derangement in liver function is self-limiting, and no patient developed any sequalae of decompensated liver disease or received any intervention.

EBV infection is an extremely rare cause of acute liver failure. One US study included a total of 1887 adults with acute liver failure, they found four cases (0.21%) were EBV-related acute liver failure.[39] Three of these cases were considered to be "probable" EBV-related as EBV was not confirmed by serological tests and liver tissue biopsy. One out of the four of the patients was immunocompromised. Two patients did not have typical symptoms of IM. In addition, acute liver failure occurred in early disease; all presented with jaundice and median time from symptom to presentation with liver disease was 13 days.

We also explored the role of abdominal ultrasound in IM. From the authors' experiences, some units will perform ultrasound to evaluate for hepatosplenomegaly in the context of deranged LFTs, however, this was not reflected in the literature as only two studies evaluated ultrasound of the abdomen. All patients were found to have splenomegaly and around half were found to have hepatomegaly. It is expected that patients would have hepatosplenomegaly as a consequence of IM, thus the advice to avoid contact sport is given to all patients. Although limited data on ultrasound, ultrasound findings did not influence management. It is worth noting that the presence of right upper quadrant pain in the context of IM may be suggestive of acalculous cholecystitis, ultrasound may be indicated here for further evaluation.[11]

Our findings also raise questions on the need for routine LFTs assessment in IM as this has the potential to lead to a cascade of unnecessary serial measurements in the community and abdominal ultrasound which has no effects on patients' outcomes.

Changing the practice with regards to serial LFTs assessment would avoid unnecessary use of limited resources, currently highlighted by national shortage of blood bottles in the UK.[40] In addition, avoid unnecessary consultations with the general practitioners.

Limitations to this systematic review include the varied methods for ascertaining diagnosis of IM and incomplete follow up in LFT assessment with varying lengths of follow-up across studies. Even within studies, there is varying interval or lack of information for repeating LFTs among individual patients. Generally, there was no standardized protocol for assessment of LFTs, thus limiting accurate assessment of time to resolution. There are also few studies on abdominal ultrasound in IM patients.

Conclusion

In IM, serial LFTs assessment is not required in immunocompetent patients with subclinical derangement in liver function. In addition, routine abdominal ultrasound is not required to evaluate for abnormal LFTs. Derangement in LFTs can persist over six months from initial presentation but is self-limiting with no evidence of long term sequalae of liver failure.

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Figure 1 Prisma flow diagram showing study selection process

Study	Selection
Chan (2003)	[?]
Gonzalez Sandana (2012)	[?]
Herbinger (2016)	[?]
Ishibashi (1987)	**X**
Massei (2001)	[?]
Mazur (2019)	[?]
Monteiro (2020)	**X**
Mygind (1976)	**X**
Rotenburg (1991)	**X**
Sohn (2017)	[?]
Son (2011)	[?]
Sridhar (2018)	[?]
#Vanderhorst (1991)	**X**
Zhang (2017)	[?]
Gadeberg (1984)	[?]
Dommerby (1986)	[?]
Baehner (1967)	[?]
Kanegane (1997)	[?]
Henke (1973)	[?]
Rosalki (1960)	[?]
Shuster (1967)	[?]
Kilpatrick (1966)	[?]
Grotto (2003)	[?]
Gao (2011)	[?]
Rea (2001)	[?]
Ginsburg (1977)	[?]
Gelb (1962)	**X**
Finkel (1964)	[?]
Wang (2013)	[?]
Topp (2015)	[?]
Baron (1965)	[?]
Evans (1948)	[?]
Case-control study # Multicentre randomized controlled trial	* Case-control study # Multicentre randomized controlled t

Table 1: Methodological assessment of included studies

Study
Chan (2003)
Gonzalez Sandana (2012)
Ishibashi (1987)
Massei (2001)
Mazur (2019)
Monteiro (2020)
Mygind (1976)
Sohn (2017)
Son (2011)
Sridhar (2018)

Study
Vanderhorst (1991)
Zhang (2017)
Gadeberg (1984)
Dommerby (1986)
Baehner (1967)
Kanegane (1997)
Henke (1973)
Rosalki (1960)
Shuster (1967)
Kilpatrick (1966)
Grotto (2003)
Gao (2011)
Rea (2001)
Ginsburg (1977)
Gelb (1962)
Finkel (1964)
Wang (2013)
#Topp (2015)
Baron (1965)
Evans (1948)
Evaluated CMV mononucleosis using CMV IgM and CMV PCR # Used EBV PCR in addition to heterophile antibodies an

Table 2 Method of diagnosis of infectious mononucleosis

Study	Proportion of raised LFTs	Maximum time to resolution of LFTs
Chan (2003) Hong Kong N = 77; Paediatric	ALT + AST – 59.2% Bilirubin – 5.6%	5.7 weeks
Gonzalez Sandana (2012) Mexico N = 163; Paediatric	Transaminases – 40.0% Bilirubin – 42.1%	NR
Herbinger (2016) Germany N = 51; All ages	AST – 64.7% ALT – 76.5% GGT – 70.6%	NR
Ishibashi (1987) Japan N = 9; Adult	Transaminases – 100%	NR
Massei (2001) Italy N = 54; All ages	ALT – 48.1% GGT – 20.4%	12 weeks
Mazur (2019) Poland N = 181; Paediatric	AST – 48.1% ALT – 49.2% GGT – 26.5%	NR
Monteiro (2020) Brazil N = 251; All ages	AST – 11.8% ALT – 15.8% GGT – 25.0%	NR
Mygind (1976) Denmark N = 36; Ages not specified	AST – 69.4%	10 weeks
Rotenburg (1991) Israel N = 82; Ages not specified	AST – 69.5% ALT – 89.0%	NR
Sohn (2017) Korea N = 149; Paediatric	ALT – 71.1%	NR
Son (2011) Korea N = 81; Paediatric	ALT +/- AST – 51.9%	NR

Study	Proportion of raised LFTs	Maximum time to resolution of LFTs
Sridhar (2018) Hong Kong N = 25; Adult	AST – 100.0% ALT – 96.0% GGT – 91.7% ALP – 56.0% Bilirubin – 0%	NR
Vanderhorst (1991) USA N = 120; Ages not specified	AST – 43.1% ALT – 40.5%	NR
Zhang (2017) China N = 95; Ages not specified	No numerical values but 'ALT, AST and GGT levels are significantly increased in IM patients compared to controls'; 'bilirubin is lower compared to controls'	NR
Gadeberg (1984) Denmark N = 10; All ages	ALT – 88.9%	>6 weeks
Dommerby (1986) Denmark N = 29; All ages	AST – 65.6% ALP – 31.0% Bilirubin – 0.0%	17 weeks
Baehner (1967) USA N = 105; Paediatrics	AST – 24.4% ALT – 35.6% Bilirubin – 15.6%	NR
Kanegane (1997) Japan N = 54; Paediatrics	No numerical values but 'mean AST and ALT values for all study patients were abnormal'	NR
Henke (1973) USA N = 776; All ages	Liver function – 53.8%	NR
Rosalki (1960) UK N = 23; Adult	AST – 78.3% ALT – 82.6% ALP – 39.1% Bilirubin – 13.0%	12 weeks
Shuster (1967) USA N = 46; Ages not specified	AST – 83.7% ALP – 82.6% Bilirubin – 17.8%	NR
Kilpatrick (1966) Germany N = 20; Adult	ALT – 65.0% ALP – 38.9% Bilirubin – 6.7%	NR
Grotto (2003) Israel N = 114; Adult	AST – 34.7% ALT – 53.2% Bilirubin – 14.9%	NR
Gao (2011) China N = 418; Paediatric	AST + ALT – 48.6%	NR
Rea (2001) USA N = 140; All ages	AST – 31.4% ALT – 61.4% Bilirubin – 5.7%	>6 months
Ginsburg (1977) USA N = 30; Paediatric	AST – 36.7% Bilirubin – 10.0%	NR
Gelb (1962) USA N = 69; All ages	AST – 83.0% ALT – 84.1% ALP – 81.4% Bilirubin – 42.9%	6 weeks
Finkel (1964) USA N = 235; Ages not specified	AST – 78.0% ALT – 78.6% ALP – 76.3% Bilirubin – 21.1%	NR
Wang (2013) China N = 287; All ages	AST – 74.1% ALT – 74.7% GGT – 52.8% Bilirubin – 12.6%	>12 days
Topp (2015) Denmark N = 95; Paediatric	ALT – 53.7% Bilirubin – 9.3%	NR
Baron (1965) UK N = 80; Ages not specified	AST – 72.5% ALP – 55.2% Bilirubin – 37.7%	6 weeks
Evans (1948) USA N = 19; Ages not specified	ALP – 42.9% Bilirubin – 36.8%	>6 weeks

Study	Proportion of raised LFTs	Maximum time to resolution of LFTs
NR – Not reported	NR – Not reported	NR – Not reported

Table 3 Proportion of raised LFTs and maximum time to resolution of LFTs of individual studies

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