

DISCUSSION AT TAG AUDIT MEETING LFT FEBRUARY 2010

1) QUESTIONNAIRE PRESENTATION

What did we mean by action limits, did we mean telephone limits or when some clinical action should be taken?

It was felt some are set far too low.

Dr Bray felt it was important to alert clinicians of high ferritin levels, greater than 1000 ng/ml.

Gamma GT should not be part of a routine LFT profile as there are a lot of isolated raised GGT results which will increase unwarranted referrals.

2) WHEN IS AN LFT NOT AN LFT? Dr Roy Sherwood

Roy Sherwood presented the case of a young RTA victim who had all biochemical liver tests abnormal at one point or another during her admission but they had nothing to do with her liver function.

23 year old female, RTA, raised bilirubin on arrival due to haematoma, raised AST raised due to skeletal muscle trauma, debulking surgery for wounds put her albumin down. She started fitting from a head injury and was given phenytoin which raised her GGT. 2 weeks later the alkaline phosphatase rose to 600 IU/L as bones were repairing and cytokine suppression had stopped.

We all need to understand the limitations of LFTs which can be abnormal in the absence of liver disease.

GGTs are raised in obesity and Type 2 Diabetes Mellitus.

In viral liver disease ALT: AST ratio is 1:1 but in liver injury by alcohol AST is greater than ALT by 2:1.

Do Macro AST and ALT exist? If there is an isolated raised AST Kings reflex a CK and 80% turn out to be muscle in origin.

Kings has a population with 30% African origin and see one sickle cell crisis per day. They have a raised bilirubin and AST and need LDH and haptoglobin added.

Alkaline phosphatase isoenzymes can be liver, bone, biliary, intestinal and placental. They are best done on fasting samples as the intestinal form is reduced. Heat inactivation is not recommended as a method. In transient hyperphosphatasaemia the shorter side chains show up on electrophoresis. This is not only seen in infancy.

Patients with extra-hepatic biliary atresia need to be referred for surgery before age 12-14 weeks or the only option is a liver transplant.

GGT has a race related reference range with Afro-Caribbean's having a normal range of twice the Caucasian range. GGT is very BMI related. At least 350 drugs induce GGT and polypharmacy may elevate GGT.

A variety of cut offs of Total Bilirubin to reflex conjugated bilirubin are used. Kings recommend greater than 50 as at that level it is possible to reliably measure conjugated levels of 15%.

Haemolysis affects bilirubin methods depending on which analyser is used and each lab should determine their own cut off.

There is no ethnicity associated with Gilbert's syndrome. There are very few instances when you need to confirm Gilbert's syndrome.

BCP is the best method to use for measuring albumin. Very high globulins 120-140 g/L are seen in HIV.

INR is used in liver transplants for monitoring liver function post surgery.

If CA 19-9 is below the limit of detection this indicates the genetic variant Lewis a- b- which does not express the tumour marker.

3) WHAT IS NEW IN BIOCHEMICAL TESTS OF LIVER DISEASE? Dr Roy Sherwood

Alpha 1 proteinase inhibitor or Pi. Kings are looking at 10 years worth of MZ phenotypes to look at presentations.

SS get lung disease later in life, SS is secreted slower.

P1 Pittsburg is a 1 amino acid substitution.

Do not quantitate AAT at Kings, ZZ can have measurable levels in serum in acute liver failure. They diagnosed a new ZZ at the age of 63.

Genotype can be done on buccal smears if the child has had a blood transfusion.

In Wilson's Cu/Cp if LFT is abnormal is a concern. 50% present with neurology. It is surprising only 1 lab offer urine copper, the penicillamine challenge test is the best discriminator. Using ICP mass spectrometry copper uptake studies can be done.

ATP7B deficiency in Wilson's

ATP7A deficiency in Menkes which is a true deficiency as is a gut defect in copper absorption.

Use genetics in family studies as there are greater than 80 mutations. In 5 Wilson's cases no mutation has been found as all exons are normal.

CDT- carbohydrate deficient transferrin. Present in childhood with neurological disorder due to glycosylation defects. Levels are 40% of normal in heterozygotes.

CDT is under discussion with the DVLA about returning a driving license for drink driving in cases over twice the upper limit for driving or with a previous conviction.

Questions?

1. Are external buccal smears accepted? Yes
2. Why is CDT not massively used? It is stable uncentrifuged for 4 days at room temperature and can be posted unspun.
CDT half-life is prolonged as have knocked side chains off and is 14 days. Suggests drinking in last 7-14 days. CDT is the equivalent for HcbA1C for alcohol misuse.
It has been used in Italy for drink driving for many years and is used in the USA and by family law. It is used in circumstances when other tests such as GGT fail, in obesity, medication and phenytoin therapy. A study is being done in Scotland in the pregnant population. In pregnancy transferrin also rises so a CDT/transferring ratio is used.
False negatives are seen for CDT, in pre menopausal women fluctuations are seen across the menstrual cycle. Need to do two, two weeks apart. Cost is an issue £12.50 compared to a GGT and MCV at £5.
Ethyl glucuronide and ethyl sulphate can also be used to detect alcohol use. They are known as the 90 hour test and can be used as a test of binge drinking.
3. Copper and caeruloplasmin are they useful in Wilson's? Cp is an acute phase protein, raised in HRT, pregnancy, oral contraceptives and steroids. If not in acute phase and not on steroids Cp is OK. If on other drugs need to use 24 hour urine copper.
Urine copper greater than 15 umol/ 24 hours before Penicillamine and > 25 umol/L post Penicillamine is 100% specific for Wilson's disease.
4. PIII NP. The British Association of Dermatologists use this in their Guidelines for methotrexate. Their patients receive 1.5 g/year and the effect is cumulative. RA patients get 10% of this dose and it will take 8 years to get toxic.
5. Can electrophoresis be used to screen for AAT deficiency? No, as get raised alpha 1 globulin with the other acute phase proteins.
6. If there is a raised ALT in a child are Caeruloplasmin and copper both required? Yes, as Wilson's can present in childhood. In adults, exclude the most likely cause first. A new diagnosis of liver Wilson's disease is very rare in patients over the age of 40.
In neurological conditions Wilson's needs excluding so cannot have an upper age limit for these patients.
Cu/Cp are used in transplant assessment.
7. Is caeruloplasmin done on acutely ill patient valid?
Yes, if undetectable but a normal result does not exclude this. 2.5% of the population will have slightly low results.

4) CLINICAL VIEW OF LFTS, OLD AND NEW by Dr G. Bray

Pattern of LFTs that are obvious strike you between the eyes. Subtle changes are not too important.

Most common liver diseases are

1. Fatty liver disease
2. Obesity
3. Non alcoholic fatty liver disease
4. Hep C suffers include Pamela Anderson, Evil Knievel, Anita Roddick

The Government has appointed a Liver Tsar Dr Martin Lombard, Royal Liverpool University Trust to tackle alcohol and the liver.

NAFLD

Patients with this die of DM, obesity, CVD and not liver disease Lots of cirrhotics are seen in Diabetes clinics
These patients can be transplanted

Liver biopsies

These have reduced in numbers, useful for prognosis or not diagnostic

Prothrombin Time

Good test
Chronic liver disease = global assessment

Abnormalities

If it is not obvious is probably not important. E.g. ALT of 85 in an over-weight patient
ALT < 100 are not seen in Dr Bray's clinic

GILBERTS

1. Raised bilirubin 20-60 umol/L
2. Can see raised bilirubin in a fasting patient with a cold
3. >100 is too high a cut off for Gilberts

Raised or rising Alkaline Phosphatase

Can be

1. Biliary
2. Metastases/ infiltration
3. Amyloid

These patients need a CT scan.

Isolated GGT

Only useful to clarify source of raised alkaline phosphatase.
It should be removed from routine liver profiles

Ferritin

Haemochromatosis is increasing in incidence. We are doing more ferritins but there are lots of missed diagnoses.

If ferritin is greater than 800 IU/L need a transferrin saturation.

If 4000 need to go on and have gene testing

If the ferritin is greater than 1000 there is a 40% risk of cirrhosis so these patients need a liver biopsy. These patients need follow up and assessment for other symptoms and varices.

CA 19-9

This should be deleted from the panel. It is OK for oncologists to use post chemotherapy and in sclerosing cholangitis. CA 19-9 is raised in obstruction

AFP

Good test. If raised and see a cirrhotic lump on scanning this is a hepatoma. This should not be biopsied if the liver is going to be resected.

Serum albumin ascetic gradient (SAAG)

Good test in patients with ascites

QUESTIONS

How often should LFTs be repeated?

In severe liver disease do them daily otherwise need a few days between tests.

Repeat as out-patient after 6 months.

33% of repeat LFTs are inappropriate

ALT Reference range

Southend quote 65 IU/L as an action limit rather than the upper limit of the reference range. The BNF quotes 3 times ULN as action limit which could be 120-200.

ALT levels < 100 are rarely significant.

HFE gene

The nomenclature used by the Cardiff molecular genetic lab is unusual and not up to date.