and a right half, and transplanted to paediatric and adult recipients, respectively. These techniques have been introduced to address the critical shortage of donor livers. The liver can be split either *in situ* in the donor, or *ex situ* after it has been removed from the donor.

Living-donor liver transplant

Living-donor liver transplants are now performed routinely in many centres throughout the world. It usually involves removing the left lateral segment from a parent for transplantation into a child. Adult-to-adult living-donor transplantation requires the removal of the right lobe of the liver from the donor and transplantation into the recipient.

Immunosuppression

Conventional immunosuppression consists of steroids, a calcineurin inhibitor (either cyclosporin or tacrolimus), and a lymphocyte proliferation inhibitor (azathioprine or mycophenolate mofetil). Induction therapy with a polyclonal antibody (ATG) or a monoclonal antibody (OKT3, Basiliximab or Daclizumab) is also an option.
All immunosuppressive agents have side-effects, and alternatives to conventional immunosuppression, such as steroid-free or calcineurin-free protocols, have been described.

Complications

Technical complications after liver transplantation are now relatively uncommon. The usual technical complications include hepatic artery thrombosis and bile duct leak or stenosis.
Most of the problems following liver transplantation are related either to inadequate immunosuppression or over-immunosuppression. The former results in acute rejection, which can be managed relatively easily with bolus doses of methylprednisolone or conversion to alternative immunosuppressive therapy.

Infectious complications related to over-immunosuppression result in significant morbidity and occasional mortality. Cytomegalovirus (CMV) infection and disease tend to be a problem in recipients who have not had previous exposure to CMV. Patients who are at high risk of CMV infection can be given prophylaxis with intravenous ganciclovir.

Lymphoproliferative disease, especially in children, seems to be related to lack of previous exposure to Epstein-Barr virus (EBV) and over-immunosuppression. The management of this complication can be difficult since the immunosuppressive therapy has to be virtually withdrawn.

Locally, tuberculosis has also been a problem, not only because of the infection itself, but also because of the side-effects of the antituberculosis drugs.

Results

The long-term results after liver transplantation are excellent (Fig.1). With better patient selection and newer, more potent immunosuppression protocols, 1- and 5-year survival figures in excess of 90% and 80%, respectively, are reported.

References available on request.

DIAGNOSIS OF PORPHYRIA IN SOUTH AFRICA

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All forms of porphyria arise from partial deficiencies in one of the enzymes of the haem biosynthetic pathway. These deficiencies may result in a specific pattern of porphyrin accumulation and a characteristic clinical syndrome. The three forms of porphyria most frequently encountered in South Africa are variegate porphyria (VP), acute intermittent porphyria (AIP) and porphyria cutanea tarda (PCT). Other forms are occasionally seen. Both VP and AIP are inherited but PCT is usually an acquired disorder associated with alcohol abuse, iron overload, oestrogen therapy, viral infection (particularly hepatitis C virus and HIV) and liver disease.

Clinically the porphyrias are characterised by two principal features: photosensitive skin disease and acute neurovisceral attacks (which may result in a potentially fatal motor neuropathy). AIP is characterised by acute attacks only, PCT by skin disease only and VP may be accompanied by both. Both VP and AIP show low clinical penetrance, and 60 - 80% of those who carry the gene remain clinically asymptomatic throughout life. It cannot be predicted which individuals will fall into this category. Essentially, these three disorders never present with symptoms or with biochemical changes prepubertally, despite inheritance of a disease-associated mutation.

It is important to diagnose VP and AIP timeously and correctly because of the risk of the acute attack. Diagnosis of PCT is important because it is often fully reversible when the underlying causative factors are correctly identified, reversed and appropriate treatment is given.

Although VP has an exceptionally high incidence in South Africa, because of the R59W founder gene, AIP and PCT are regularly encountered and frequently misdiagnosed or misidentified as VP. The diagnosis of AIP and PCT may also be missed and delayed.
Every South African doctor must apply a sensible diagnostic approach to:

- establish whether a patient has porphyria
- to assess whether the presenting symptoms are indeed caused by the porphyria

It is dangerous to diagnose porphyria on clinical grounds alone and laboratory investigations must always be requested.

- type the porphyria correctly and so provide appropriate advice for the patient and family.

More prescriptive instructions on the diagnosis of porphyria are available on our website: **web.uct.ac.za/depts/porphyria**.

Diagnosis of the porphyrias

Theoretically, a diagnosis could be made clinically, by porphyrin metabolite studies, or, except in the case of acquired PCT, by enzyme assay and genetic testing.

It is dangerous to diagnose porphyria on clinical grounds alone and laboratory investigations must always be requested. Thus, metabolite measurements (urinary porphobilinogen/delta-aminolaevulinic acid (PBG/ALA)), faecal, urinary and plasma porphyrins or plasma fluorescence emission spectroscopy, as appropriate) are essential for the diagnosis of clinically overt porphyrias, because symptoms cannot be ascribed to porphyria unless specific patterns of overproduction of porphyrin precursors/porphyrins are demonstrated. Enzyme measurements are not essential and may be misleading owing to overlap between normal and disease ranges. Demonstration of a disease-specific mutation in the appropriate gene identifies porphyria (e.g. the R59W mutation in VP) but, by itself, gives no indication of disease activity.

Two new techniques have greatly improved and simplified the diagnosis of porphyria in South Africa over the last 10 years – the advent of R59W gene testing for VP and plasma porphyrin fluoroscanning, both of which can be performed on a single blood sample.

Diagnosis when porphyria symptoms are present

It is axiomatic that porphyria patients who are symptomatic always have disturbed porphyrin metabolism. (One cannot have symptoms and negative tests – provided that the right tests are applied and correctly done!) Under these circumstances, biochemical testing is the appropriate first investigation.

If symptoms of an acute attack are present or suspected

An acute attack of porphyria is always accompanied by increased urinary excretion of ALA and PBG. Examination of urine for excess PBG is *the* essential investigation in patients with a suspected attack of acute porphyria. Measurement of urinary porphyrin by itself is unhelpful and may be misleading. Although concentrations are usually increased in acute porphyria, mainly owing to *in vitro* polymerisation of PBG to uroporphyrin, increases also occur in non-acute porphyrias, hepatobiliary disease, alcohol abuse, infections and other common disorders.

Urinary PBG is best analysed in a fresh, random sample (10 - 20 ml) collected without any preservative but protected from light. Elevated PBG can be qualitatively screened for using the Watson-Schwartz reaction, in which PBG reacts with Ehrlich's aldehyde to produce a red colour. (Urobilinogen also reacts with Ehrlich's aldehyde, and the two are distinguished by the addition of chloroform, since urobilinogen is soluble in chloroform while PBG is not.) The test is rapid, can be done at the bedside, is widely used and is offered by all pathology services in South Africa.

Where the test is positive, or where it is unhelpful in the face of strong clinical suspicion, PBG in urine should be confirmed by quantitative measurement, typically by spectrophotometric measurement of the red product formed by its reaction with Ehrlich's reagent after removal of urobilinogen and other interfering substances by anion exchange chromatography. Such tests are available in specialist porphyrin laboratories such as the one at the University of Cape Town (UCT).

If photosensitive skin disease is present

Plasma fluorescence emission spectroscopy (fluoroscanning) is very useful as a front-line test in all commonly encountered porphyrias in South Africa, because a maximum peak emission at 624 - 627 nm establishes the diagnosis of VP. In PCT (as well as in AIP), an emission peak at 619 - 620 nm may be present. This test is available in the UCT laboratory and relies on the presence of a peptide-porphyrin complex in saline-diluted plasma of VP patients, visible as an emission maximum peak when excited at a fixed wavelength of 405 nm using a fluorescence spectrometer fitted with a red-sensitive photomultiplier. For plasma porphyrin fluoroscanning, 5 ml of ethylenediaminetetra-acetic acid (EDTA)-anticoagulated blood is needed.

We have shown that in the South African population, plasma fluoroscanning is both more sensitive and specific than faecal porphyrin chromatographic analysis for the diagnosis of VP. However, in all cases where a

plasma fluoroscan is positive (and in negative cases where the index of suspicion remains high), quantitative porphyrin metabolite measurements (in urine, faeces or blood, as appropriate) follow to confirm the type of porphyria (VP or PCT) and to establish a level of porphyrin disease activity.

Furthermore, in the South African setting, any patient yielding biochemical results suggestive of VP should be tested for the presence of the R59W gene mutation (see below).

Diagnosis when porphyria symptoms are not present, but a family or clinically suggestive history is present

Although our experience suggests that plasma fluoroscanning may in some instances identify carriers of a porphyria-causing mutation prepubertally, neither such scanning nor porphyrin metabolite analysis is sufficiently sensitive for the exclusion of the familial carrier state, particularly in children. Therefore one should not rely on these techniques in excluding inheritance of porphyria in asymptomatic family members, particularly in childhood. We recommend that DNA-based techniques be used for this; also in asymptomatic individuals of any age or in those in remission (individuals in whom previous symptoms of porphyria have resolved), as urinary, faecal and plasma porphyrin concentrations may return to normal during remission.

In South Africa, VP gene testing for the R59W mutation is well established and routinely available in a number of laboratories. This is a particularly useful tool as the single R59W mutation in the protoporphyrinogen oxidase gene is responsible for 94% of all cases of VP in this country. For such testing, 5 ml EDTA-anticoagulated blood is best.

DNA testing for the relatively small number of other VP-causing mutations, responsible for the remaining 6% of VP patients, is also available as a research service on request.

We have also established the specific gene mutation responsible for AIP in a small number of South African AIP families and, although not available as a routine service, such testing may be arranged as a research service.

Conclusion

R59W gene testing and plasma fluoroscanning offer significant increases in both sensitivity and specificity of testing for porphyria. Nevertheless, we recommend that R59W DNA testing must either be preceded or followed by plasma porphyrin fluoroscanning and accurate biochemical quantitation of porphyrin metabolites, if and as appropriate. Any laboratory that merely provides a negative R59W result for VP when asked to exclude porphyria and does not proceed to the porphyrin quantitation essential for excluding all types of porphyria, is providing an incomplete and potentially dangerous service, as other forms of porphyria, including R59W-negative porphyria, may be missed. The R59W test is only appropriate as a single test under two circumstances:

- for detection of VP carriage in a family known to carry the R59W mutation
- if the result is positive in a patient with characteristic skin disease.

Specimens required

For DNA testing: 5 ml EDTA blood. This must not be frozen and should reach the laboratory within 48 hours, preferably not on a weekend.

For plasma porphyrin fluoroscanning: 5 ml EDTA blood. Plasma should be separated within 24 hours or as soon as practical to avoid contamination with haemoglobin, which may interfere with the porphyrin analysis.

For other porphyrin biochemical testing: stool – 10 g (non-liquid); urine – 30 ml random sample (no preservative); blood (heparinised) – 10 ml. All samples must be in sealed, light-protected containers.