

Inherited Metabolic Disease Acute Liver Failure

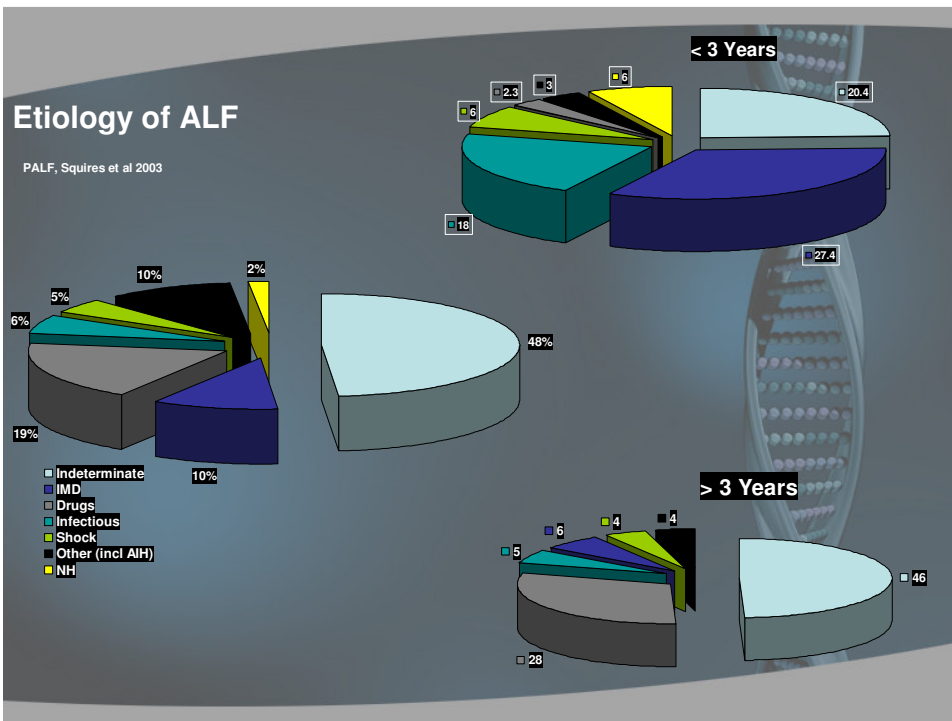
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Outline

- Why is it important to make the diagnosis.
- Causes of ALF in childhood.
- IMD causing ALF.
- When to suspect an IMD.
- What investigations to do.
- What treatment to start.

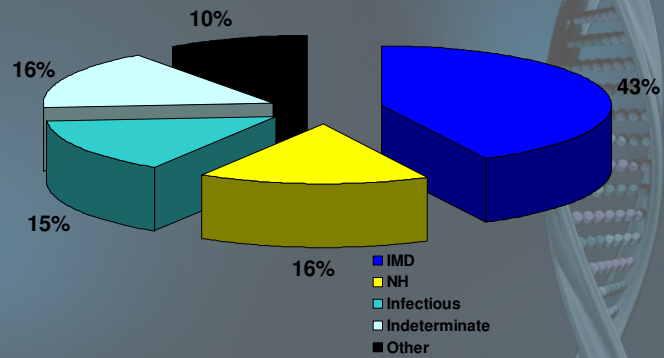
Importance of the diagnosis

- Effective treatment available for some (galactosaemia, tyrosinaemia type1).
- Prevention of disability (hypoglycaemia, hyperammonaemia).
- Genetic counseling.
- Determining the appropriate level of care.



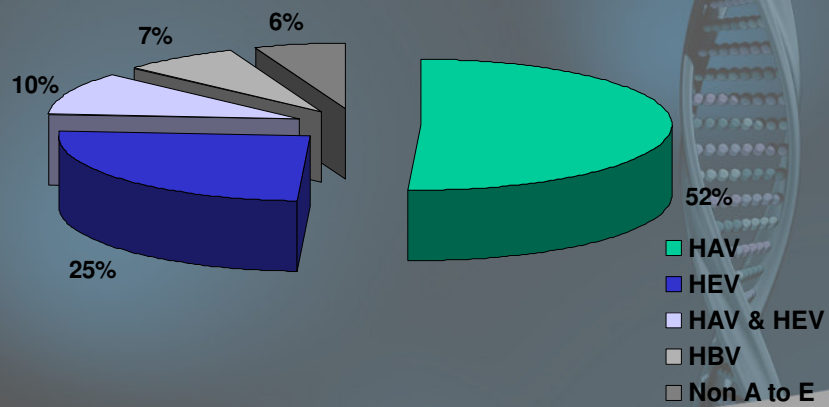
Etiology of ALF < 1 year

Durand 2001



Etiology of ALF in Developing Countries (India)


Poddar 2002



IMD Presenting with ALF

< 3 Years

PALF, Squires et al 2003
n=23




| | |
|-------------------------------|---------|
| • Respiratory chain defects | 7 (30%) |
| • Tyrosinaemia | 4 (17%) |
| • Fatty acid oxidation defect | 4 (17%) |
| • Galactosaemia | 2 (9%) |
| • Mitochondrial disorder | 2 (9%) |
| • Alpha-1-antitrypsin def. | 1 (4%) |
| • Fructose intolerance | 1 (4%) |
| • Nieman Pick C | 1 (4%) |
| • Urea cycle defect | 1 (4%) |
| • Neonatal haemochromatosis | 6 |

IMD Presenting with ALF

> 3 Years

PALF, Squires et al 2003
n= 13



| | |
|--------------------------|---------|
| • Wilson disease | 9 (69%) |
| • Mitochondrial disorder | 2 (15%) |
| • Reye syndrome | 1 (8%) |
| • Urea cycle defect | 1 (8%) |

IMD Causing ALF

| Neonates | Infants and Young Children | Older Children |
|--|---|--|
| <ul style="list-style-type: none"> •NH •Mitochondrial disease •Galactossaemia •Tyrosinaemia •Nieman Pick Type C •Fatty acid oxidation defects (FOD) •HFI •Urea cycle defects | <ul style="list-style-type: none"> •Galactossaemia •Tyrosinaemia •Mitochondrial disease •Nieman Pick Type C •FOD •Hereditary fructose intolerance •Urea cycle defects •Alpha-1-antitrypsin deficiency •CDG | <ul style="list-style-type: none"> •Wilson's disease •Other <ul style="list-style-type: none"> –Mitochondrial disorders –Urea cycle defects |

Dilemmas in Making the Diagnosis in Africa

- IMD relatively rare
- Many causes of ALF
 - High burden of infectious diseases in Africa
- Features of ALF overlap with those of IMD e.g. hypoglycaemia, encephalopathy, increased NH_4
- Often poor history
- Antenatal Clinic attendance poor
- Low level of awareness among health care workers
- Diagnostic facilities limited
- Limited expertise

When to suspect an IMD in ALF

- Family history
- Unexpected early onset
- Associated signs/symptoms
 - Metabolic
 - Acidosis
 - Hypoglycaemia
 - Neurological
 - Dysmorphic
 - Recognised clinical pattern
- Association with feeds (e.g. Hereditary fructose intolerance)

What investigations should be done

- Investigations appropriate for ALF
 - Include the following:
 - Clotting profile
 - Liver Biochemistry
 - low or moderate increase in enzymes
 - neonatal haemochromatosis
 - Fatty acid oxidation defects
 - Mitochondrial respiratory chain defects
- NH_4
- Lactate/pyruvate
- Fe, transferrin, ferritin

What investigations should be done

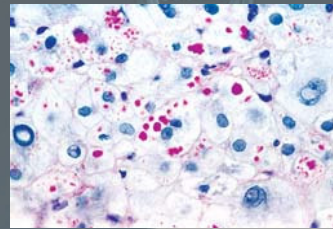
- Urine reducing substances/chromatography
- Urine organic acids and amino acids
 - Succinyl acetone
- Urinary copper
 - 24 hour/penicillamine challenge?
 - Diagnosis of Wilson Disease difficult in ALF

What investigations should be done

- Serum amino acids, carnitine and acylcarnitine
- Serum Alpha-1-antitrypsin
- Serum alpha-fetoprotein
- Galactose-1-phosphate uridyl transferase
- Hypopituitarism

What investigations should be done

- Bone marrow biopsy
- Imaging
 - Brain
 - MRI (iron)
 - liver
- Ophthalmology
- Liver biopsy
 - Remember tissue for EM
 - Copper content
 - PM tissue
- Skin biopsy for fibroblasts



What initial treatment

- Supportive treatment
 - Glucose
 - Coagulopathy
 - Infection (including fungal infections)
 - Fluids & electrolytes
 - Encephalopathy and cerebral oedema
- Diet
 - Lactose free (suspected galactosaemia)
 - Fructose free (HFI)
 - Restrict protein intake

What specific treatment

- Galactose free diet
- NTBC
- Fructose free diet
- Antioxidant “cocktail”

Liver transplantation

- Indicated where transplantation will reverse/improve the disease
- Contra-indicated where there is irreversible extra-hepatic disease
 - e.g. Mitochondrial disease