Editorial

Genetics in paediatric liver disease

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Genetics (genetic constitution of an individual, group, or class) is a branch of biology that deals with heredity, especially the mechanisms of hereditary transmission and the variation of inherited characteristics among similar or related organisms.[1] Genetic professionals include medical geneticist, genetic counselor, laboratory geneticist and nurse geneticist.[2]

Clinical geneticist tries to identify the etiology, mode of inheritance and the risk that a similar disorder may occur in the affected childs' siblings. Five different categories are required for classification of the patients' disorder. Single gene mutations account for 6% of the children with congenital anomalies, chromosomal disorders 7.5%, multifactorial inheritance 20%, and disorders with unusual pattern of inheritance 2 to 3%, while teratogenically caused conditions are 6%.[3] Hence, prenatal diagnosis is necessary when familial, maternal or foetal conditions, may result in malformations, chromosomal abnormality or genetic disorders.

There are studies related to the degeneration of the retina such as in the syndromic entity of BBS (Bardet-Biedl syndrome) and other ciliopathies.[4] However, studies on genetic disorders of paediatric liver disease from Pakistan are few if any.

Disorders of the liver are common causes of chronic illness in childhood, affecting approximately one of every 8,000 children. Most childhood liver diseases are congenital (present at birth), and may be caused by a variety of genetic abnormalities, structural malformations, or prenatal infections. In addition, older children and teenagers may be affected by some acquired disorders seen in adults. Paediatric patients account for about 12.5% of liver transplant recipients.[2,3]

Genetics in liver disease is an important topic. Various paediatric liver diseases in our setup, remain undiagnosed and are managed symptomatically and a diagnosis based on clinical suspicion, radiology, and lab parameters only, rather than a confirmatory diagnosis based on scientific evidence such as genetic analysis of liver tissue, blood/serum etc.

Over the years importance of genetic diagnosis of various diseases especially related to hepatology is shown in the table. However, we have had to face serious deficiencies in our lab analysis, as very few experts and labs are available to do the special diagnosis, required for genetic evaluation in Pakistan. Various diseases have been

Table.

Disorder	Related genetic basis
Neonatal hepatitis and biliary atresia	Associated with trisomy 17-18 syndrome and trisomy 21
Familial intrahepatic cholestasis	PFIC1/AR/18q21-22/ATP8B1/F1C1 PFIC2/AR/2q24/ABCB11/BSEP PFIC/AR/7q21/ABCB4/MDR3/MDR3
Alagille syndrome	AD/mutation in JAG1 or Notch 2
Autoimmune hepatitis	AIH type 1, HLA DR3 (DRB0301), AIH type 2, HLA DR7 (DRB10701)
Sclerosing cholangitis	HLA class II, DR3,DQ2 and DR6,DQ6
α 1-Antitrypsin defiency	serum α 1-AT phenotype, PIZZ
Cystic fibrosis	gene on long arm of chromosome 7
Galactosemia, Hereditary fructose intolerance	AR
Type 1a Glycogen storage disease	defiency of D-glucose-6-phosphatase Chromosome 17q21
Type III Glycogen storage disease	gene localized to chromosome 1p21
Type IV Glycogen storage disease	gene localized to chromosome 3p12
Wilsons disease	long arm of chromosome 13, ATP7B
Heriditory hemochromatosis	AR, HFE gene encodes MHC class 1-like molecule
Tyrosinemia	AR , mutation in the FAH gene
Gauchers disease	AR
Niemann –Pick A and B	AR, gene sphingomyelin phosphodiesterase-1 (SMPD1) Chromosome 11p 15,4-p15.1, more than 50 mutations
Fabers disease	AR, mutation - gene lysosomal acid ceramidase (ASAH)
GM1 Gangliosidosis	AR, mutation in ?-galactosidase gene (GLB1), maps to chromosome 3p21, 33
Niemann-Pick disease type C	AR, mutation NPC1 and NPC2, genes map to chromosome 14q24.3, mutations 130, identified
Fucosidosis	gene for α-L-fucosidase (FUCA1)
α-Mannosidosis	AR, gene α- Mannosidosis (MANB)
Sialidosis	AR, gene for lysosomal neuraminidase (NEU1)
Galactosialidosis	AR, gene protective protein/cathepsin A (PPCA) Chromosome 20q13.1
Pompes disease	AR, gene acid -glucosidase (GAA) maps to chromosome 17q25.2-q25.3
Fatty acid oxidation defects.	Molecular DNA common gene mutations, MCAD K329E and LCHAD E474Q mutation.

highlighted in the table, they are but a few which have been documented in literature. We may miss out on all of them due to which diagnosis given to patients is incorrect and awareness among the general population regarding specific disease related to inheritance is missed.

A group of children has been identified with Bile canalicular transport disorders (Bylers disease or syndrome. Another term used for this condition is Progressive familial intrahepatic cholestais (PFIC). Three types have been described PFIC 1, 2 and 3. Genetic diagnosis and differentiation is possible (Table). The two infantile disorders with low serum GGT are ATP8B1(FIC-1) deficiency PFIC-1 and bile salt export pump (BSEP) deficiency (PFIC-2). However, in PFIC-3 with MDR3 deficiency have intrahepatic cholestasis, but an elevated GGT.[5,6]

Patients with biliary atresia comprise 50% of the paediatric patients who require a liver transplant. Other disease states that progress to end-stage liver disease in paediatric patients include metabolic disorders and progressive intrahepatic cholestasis. Examples of metabolic derangements include Wilsons disease, alpha 1-antitrypsin deficiency, tyrosinaemia, and haemochromatosis. Other metabolic disease states leading to hepatic dysfunction include Crigler-Najjar syndrome, glycogenosis, hyperoxaluria, metabolic respiratory chain deficiencies, familial hypercholesterolaemia, and methylmalonyl aciduria.[7]

The need of the hour is to establish full fledged genetic lab with appropriate facilities conducive to the need of the general public and not private, only. This can initially only be achieved in collaboration with international institutes and funded by NGOs or government. Our research is centered on HCV, HBV and communicable disease to name a few. However, as the Table indicates innumerable liver diseases are genetic born and hence future pregnancies can be prevented by appropriate counseling to the parents.

Confidentiality should be maintained in genetic testing and keeping in mind the child's interest at the foremost. Guidelines regarding genetic testing are available by the American society of human genetics and American college of medical genetics.[2]

Hence, we as clinicians/researchers in collaboration with Medical and laboratory geneticist should focus on prevention. This can be achieved by counseling families with affected children so that future affected children can be avoided. In the long run, this will save the budget of the individual families and the government. Genetic counseling sessions with the family should include a discussion of the specific diagnosis/condition, various differential diagnosis when a specific diagnosis cannot be made, knowledge of the natural history of the condition, genetic aspects of the condition and recurrence risk, prenatal diagnosis and prevention, therapies and referral, support groups to help the affected family and follow up to keep up to date with new developments of the particular disease. Counseling should be non directive i.e. family should have a choice about reproduction and to determine what is right for them.[8] Above all, the information is provided in understandable terms and outlines the range of options available to them.

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