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Diabetes in Childhood

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In earlier years, children were more vulnerable to communicable diseases like malaria, pneumonia, diarrhea, and other seasonal infectious diseases. Non-communicable diseases (NCDs) result from the interaction of genetic, physiological, environmental and behavioral factors, and present a significant burden on individuals, communities and economic resources. Indeed, children, adolescents and young adults are increasingly affected by NCDs - a population which remains hidden from global surveillance, targets and priorities. One of the major NCDs that affects children is diabetes.

There are many forms of diabetes in children, which should be differentially diagnosed for the ease of treatment and management. Type 1 diabetes (T1D), type 2 diabetes (T2D), maturity onset diabetes of the young (MODY), neonatal diabetes (NDM) and fibro-calculous pancreatic diabetes (FCPD) are some of the more common forms of diabetes reported in India.

T1D develops due to autoimmune destruction of beta cells so daily insulin shots are needed for survival; it is one of the more prevalent forms of diabetes in children and young adults. T2D is marked by insulin resistance, and there may even be hyperinsulinemia in the initial stages, but beta cell loss develops over time. Previously unheard of in children and teens, T2D is now being diagnosed more often in young people, due to the rising tide of childhood obesity. MODY has several subtypes, but is commonly caused by a variant in the HNF1A, HNF4A or GCK genes. A family history of diabetes traced to three or more generations was considered characteristic, but with rising obesity, this may occur with T2D also. It is useful to diagnose MODY, as some subtypes may be controlled by oral drugs and insulin can be stopped. NDM is caused by genetic defects in pancreatic insulin secretion; some of these patients, especially those with variants in the KCNJ11 and ABCC8 genes, may respond to oral drugs. Therefore, genetic testing is desirable, in case a specific mutation can be identified. FCPD is found in lean young adults belonging to lower socioeconomic strata, presenting with history of recurrent abdominal pain and steatorrhea, and usually severe hyperglycemia. [Unnikrishnan & Mohan;2021]. Figure 1 presents the differential diagnosis of childhood diabetes in India.

The first national-level multicentric clinic-based registry of youth-onset diabetes from India was started in the year 2006 by ICMR: the ICMR Young Diabetes Registry (ICMR YDR). Chennai is one of the major contributors of young diabetes cases to the nationwide data pool. In the Chennai data submitted to the ICMR YDR, we found 1429 children were diagnosed below the age of 15years [Amutha A et al; 2021]. Among them, 88.2% (n=1261) had T1D, 7.6% (n=108) had T2D and 4.2% (n=60) were other diabetes types like FCPD, MODY and other genetic syndromes etc.

The genetic syndromes associated with diabetes include:

- Wolcott–Rallison syndrome (WRS, OMIM 226980) is a rare autosomal recessive (AR) multisystem disorder due to homozygous mutations in EIF2AK3 (PERK), the gene encoding the eukaryotic translation initiation factor-2α kinase 3. WRS is characterized by permanent neonatal diabetes mellitus (PNDM), epiphyseal dysplasia, hepatic, and renal dysfunction [Jahnavi et al 2013].
- Wolfram syndrome, also called DIDMOAD, is a rare AR genetic disorder marked by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness as well as various other possible defects.
- Usher syndrome is a progressive condition characterized by partial or total hearing loss (inner ear abnormalities) and vision loss.

- Ehlers-Danlos syndrome is a group of inherited disorders that affect connective tissues, primarily skin, joints and blood vessel walls.
- Alström syndrome is characterized by a progressive loss of vision and hearing, dilated cardiomyopathy, obesity, T2D, and short stature.
- Down syndrome or trisomy 21, has a higher risk of developing diabetes, along with characteristic physical features and developmental delay.
- Rabson–Mendenhall syndrome is a rare AR disorder characterized by severe insulin resistance.
- Thiamine-responsive megaloblastic anaemia syndrome (TRMA) is an AR disorder due to abnormalities in active thiamine uptake into cells; features include megaloblastic anaemia, mild thrombocytopenia and leukopenia, sensorineural deafness and diabetes.

Figure 2 presents the regional variation in the distribution (%) of diabetes cases in YDR. In the registry, we found a significant variation in the distributions of T1D and T2D from the registered cases from Regional Collaborating Centers (RCCs) like Chennai (42.5 vs. 39.2%) and Dibrugarh (44.5 vs. 43.1%) where equal proportion of T1D and T2D cases were registered with age at diagnosis $\leqslant$25 years. However, this is not the case in other RCCs, where T1D contributed major proportion of their total cases registered [Praveen PA et al; 2021]. Similarly, from Chennai, there were variations in the data collected for e.g., government hospitals mostly had T1D, whereas private hospitals had a large number of T2D and Gestational Diabetes participants [Amutha A et al; 2021]. Even though, the registry data provide us with a wide spectrum of childhood onset diabetes from the geographic based regional centers, the observed intra and inter regional variations in YDR should be interpreted with caution as the distribution of cases might be due to the nature of the reporting centres (e.g., referral centres, speciality clinics, paediatric clinics, etc.) and patient's health care seeking behaviour [Praveen PA et al; 2021].

The bottom line is that, all children with diabetes need not have T1D: in the presence of any atypical clinical features, the aforementioned types of diabetes and syndromes should be thought of, and investigated as necessary.

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Figure 1: Differential diagnosis of childhood diabetes in India

Modified from: Unnikrishnan R, Amutha A, Mohan V. Type 2 diabetes mellitus in childhood and adolescence. In: IAP Speciality Series on Pediatric Endocrinology. (2nd edition). Shah NS, Rao S (eds). IAP National Publicaiton House, Gwalior, Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, 2013; 147-153.

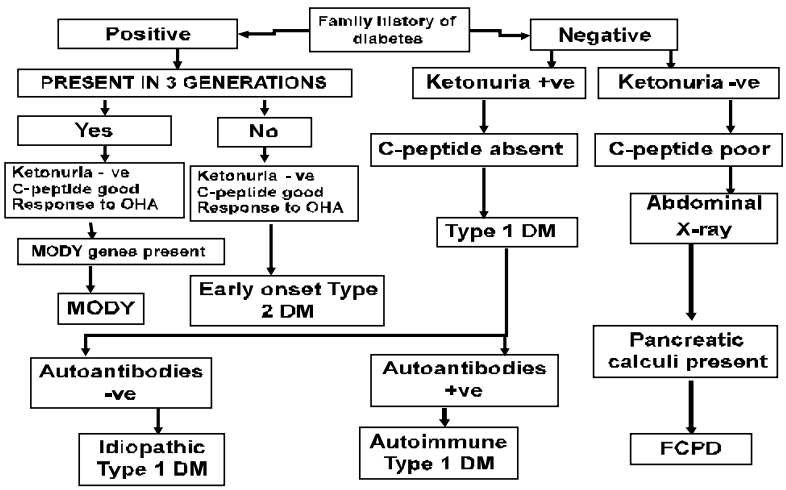

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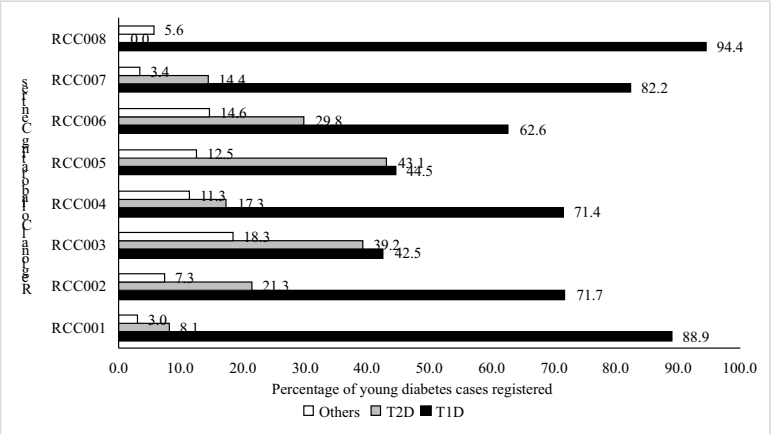
Figure 2: Regional variation in the distribution (%) of diabetes cases in YDR registry.



RCC01—All India Institute of Medical Sciences (AIIMS), New Delhi; RCC02—University College of Medical Sciences (UCMS), New Delhi; RCC03— Madras Diabetes Research Foundation (MDRF), Chennai; RCC04—SCB Medical College, Cuttack; RCC05—Assam Medical College (AMC), Dibrugarh; RCC06—KEM hospital, Mumbai; RCC07—P.D Hinduja hospital, Mumbai; RCC08—Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh

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