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10th World Summit on IMMUNOLOGY AND IMMUNOTHERAPY

August 30-31 2022 | Webinar

Monogenic Inborn errors of Immunity in patients of Autoimmune diseases

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Abstract

Objectives: To analyse the clinical data, antibody profile, immunophenotype and exome sequencing reports of children with autoimmune diseases (AID) that may serve as a marker for underlying Primary immune regulatory disorders (PIRD). Estimate prevalence of different PIRD in various AID. Estimate prevalence of different AID in various PID. Here-in we present a case series of 56 cases who presented with multiple AID.

Methods: This is a prospective and retrospective cohort study that evaluated 56 patients with AID referred in the year 2020-2021. Their clinical data was evaluated and exome sequencing was performed.

Results: The median age of onset of AID was 4.25 years. Male to female ratio was 1.07. 16/56 (29%) were born of consanguineous marriage. 8/56 had a family history of at least 1 AID. The AID referred to immunology department were haematological (42%) > GI (16%) > Skin (14%) > Endocrine (10%) > Rheumatological (9%) > Renal (6%) > Neurological (2%). 6/51 (11.7%) had ANA+ excluding 5 children with lupus. 5/56 patients met the JMF criteria for PID. 46/56 children had received steroids. 10 received rituximab for their AID. 14/56(25%) had CD19 lymphopenia, 18/56(32%) had CD4 lymphopenia, 7/56(12%) had CD8 lymphopenia. 17/56 (30%) had hypogammaglobinemia, 3 were found hypogammaglobinemic after Rituximab. 28/56 (50%) had pathogenic variants among PIRD genes, 6 had variants in LRBA, 3 had STAT1 GOF, 2 with SPENCDI. Other PIRD genes identified were NFKB1, NLRP12, CARD11 GOF, STAT3 GOF, RTEL1, NCF2, ATM, RAG1, BTK, IL12RB1, CR2 and CD55 micro deletion/CHAPEL, FOXP3, CTLA4, PIK3CD, CD40L, ADA2. 9 had VUS in PIRD genes related to phenotype, 1 had VUS in non PIRD gene related to phenotype, 11 had VUS unrelated to phenotype and 5 had no variants. These 28 patients had 42 autoimmune diseases amongst which hematological was most common (50%) > GI (16%) > Endocrine (9%) > Skin (11%) > Rheumatological (7%) > Renal and neurological (1%). These 28 children constituted 33% of those with lymphopenia, 57% of those with B lymphopenia,38% of those with CD4 lymphopenia, 28% of those with CD8 lymphopenia and 41% of those with hypogammaglobinemia. JMF criteria had specificity of 100% in identifying PIRD but sensitivity was only 17%.12/28 of these children were offered transplant. 7 were started on sirolimus, 2 on abatacept, 5 on baracitinib after diagnosis. 3 have died [LRBA (1), STAT1 GOF (2)]

Conclusion:

50% of children with AID have underlying PIRD, rising to 58% for those with haematological AID. LRBA, STAT1 GOF and SPENCDI were the most common PIRD. Routine immunological tests and JMF criteria for diagnosing PIRD are unreliable especially because vast majority are on steroids and other immunomodulatory drugs. Early diagnosis with exome sequencing alters the prognosis and opens
new therapeutic avenues.

Biography

Dr. Vaishnavi is a junior consultant (Paediatric Immunology) at Bai Jerbai Wadia Children's Hospital, Mumbai under the aegis of Maharashtra University of Health Sciences (MUHS). She is looking forward to further specialize in the field of Paediatric Immunology. She is a post graduate (MD - Paediatrics) from Seth G.S. Medical College associated with King Edward Memorial Hospital, Mumbai. She has completed her undergraduate degree (MBBS) from B.J. Medical College and Sassoon Hospital, Pune. She was also handpicked for ICMR's Omix course in Biomedical and clinical research at NIRRCH and has completed the same.

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