Coexistence of Two Rare Autosomal Recessive Disorders: Activation-Induced Cytidine Deaminase Deficiency and Sjogren-Larsson Syndrome

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activation-induced cytidine deaminase (AID, gene AICDA) is a DNA editing protein which plays an important role in three major events of immunoglobulin (Ig) diversification: somatic hypermutation, class switch recombination (CSR) and Ig gene conversion [1]. Inborn errors in AICDA result in the rare autosomal-recessive (AR) primary immunodeficiency disorder (PID) hyper-IgM syndrome type 2 (HIGM2 or AID deficiency, MIM#605258), which is characterized by normal or elevated serum IgM levels, absence of IgG, IgA, and IgE, and results in lymphoid hyperplasia and profound susceptibility to bacterial infections [1]. Sjogren-Larsson syndrome (SLS, MIM#270200) is also a rare AR disorder, manifested by a clinical triad of ichthyosis, mental retardation and spastic diplegia. It is caused by a deficiency of fatty aldehyde dehydrogenase (FALDH), an enzyme that induces oxidation of fatty aldehyde to fatty acid and is encoded by the ALDH3A2 gene [2].

We report here the coexistence of HIGM2 and SLS in the same consanguineous Arab parents [Figure 1A]. Since early childhood he suffered from recurrent otitis media and pneumonia. During the first year of life, his skin became dry and he was diagnosed with ichthyosis. His motor and language development was delayed, as he started walking independently at 3.6 years and...
speak only four words at the age of 4 years. He underwent bilateral tonsillectomy and adenoidectomy at age 1 year due to obstructive sleep apnea caused by enlarged tonsils and adenoids. On physical examination he was noted to have generalized xerotic skin with lichenified, brown and hyperkeratotic plaques affecting the neck, axillae, abdomen, and popliteal fossae [Figure 1B]. Nails and teeth were normal. Neurological examination revealed increased deep tendon reflexes in his lower extremities and a clumsy and unstable gait without muscle wasting, consistent with spastic diplegia. At the age of 2 years he was found to have hypogammaglobulinemia, with low IgA (25 mg/dl), normal range 70–400 mg/dl), low IgG (308 mg/dl, normal range 700–1600 mg/dl), normal IgE and normal IgM levels (115 mg/dl, normal range 40–230 mg/dl). The patient’s complete blood count was within normal limits. He has been maintained on monthly intravenous immunoglobulin (IVIG) therapy with clinical improvement. Any attempt to discontinue the treatment was followed by recurrence of the infections. Although a primary immunodeficiency disorder (PID) was suspected, his diagnosis was unclear and he was referred to our medical center for further evaluation.

The elder brother of PIV1 is a 7 year old boy who has suffered from ichthyosis since infancy and also has a clumsy and unstable gait without muscle wasting, consistent with spastic diplegia. His brother, PIV2, could have been oligoimmune due to hypogammaglobulinemia and ichthyosis. In this study we present a family with two rare and unrelated AR disorders. The combination of hypogammaglobulinemia with lymphoid hyperplasia, ichthyosis and neurological abnormalities has not been previously reported. Its coexistence in a single patient (PIV1), originating from a consanguineous family, raised the possibility that a novel monogenic AR disease may be responsible for this unusual phenotype. His brother, PIV2, could have been oligosymptomatic for this disorder. However, the unique clinical association of ichthyosis, mainly affecting flexures, with spastic diplegia seen in SLS, led us to suspect that PIV1 was manifesting a combined phenotype of SLS and a PID. Meticulous clinical characterization together with WES allowed us to focus our search on specific genes and show that the cause of PIV1’s immunological, cutaneous and neurological abnormalities stem from two separate homozygous mutations in AICDA and ALDH3A2 genes, causing a combined phenotype of HIGM2 and SLS, respectively. PIV2 was shown to suffer only from SLS.

To the best of our knowledge this is the first description of an associated phenotype of HIGM2 and SLS. In HIGM2, there is a defect in the ability of B cells to undergo class switch recombination (CSR) and somatic hypermutation. AID is expressed by B cells and deaminate cytosines from exposed single strands of DNA, which are essential for triggering both CSR and somatic hypermutation. The absent or low serum IgG, IgE and IgA levels in these patients can be explained by the intrinsic inability of activated B cells to undergo class switch recombination [3]. Patients suffering from HIGM2 tend to develop lymphoid hyperplasia. This is thought to result from continuous proliferation of B cells by antigen in the absence of successful Ig somatic mutation [3]. The patient described here (PIV1) presented an immunological phenotype consistent with HIGM2 syndrome. He was found to be homozygous for a novel nonsense mutation in AICDA, expected to produce a truncated non-functional protein, resulting in AID deficiency.

SLS results from a deficiency of fatty aldehyde dehydrogenase, encoded by ALDH3A2, which metabolizes fatty aldehydes to fatty acids. Defective fatty aldehyde causes accumulation of fatty aldehydes, fatty alcohols and related lipids in keratinocytes. This results in abnormal formation of lamellar bodies in the stratum granulosum and impaired delivery of their precursor membranes to the stratum corneum. The epidermal water barrier is disrupted and ichthyosis is observed clinically, affecting mainly the neck, lower abdomen and flexures [4]. PIV1 and PIV2 presented flexural ichthyosis accompanied

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by spastic diplegia and in PIV1 also by developmental delay due to a homozygous mutation in \textit{ALDH3A2}, which confirmed the diagnosis of SLS in both patients.

In populations where consanguinity is common, a corresponding increase in the frequency of AR diseases is usually found due to increased risk of homozygosity for ancestral haplotypes, which harbor pathogenic alleles. Homozygous regions associated with recessive disorders may reach approximately 11% of the genome in inbred populations [5], enabling two rare diseases to present in a single patient or pedigree. The clinical diagnosis of this state could be misleading. Careful and detailed clinical evaluation combined with the WES technique is crucial for deciphering this complex phenotype.

In conclusion, we believe this to be the first report of coexisting HIGM2 and SLS in one patient and family, revealed by the combination of a detailed phenotype and the use of WES. It further demonstrates the growing importance of WES as a powerful technology in the service of clinical genetics.

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**References**


Poor nutrition during the early years of life can have severe consequences for subsequent skeletal, immunological, and intellectual development. Blanton et al. reviewed the evidence showing that undernutrition is not caused by food insecurity alone. Other factors range from the length of the breastfeeding period and the availability of milk oligosaccharides, enteropathogen exposure, and enteric dysfunction marked by villus atrophy and loss of gut barrier function. Unfortunately, nutritional restoration with or without antibiotic treatment may not be effective in the longer term. Differences in the succession of microbial establishment and maturity can explain much of family discordances in nutritional status. The evidence indicates that microbiota-directed therapeutics could be a promising route to nutritional restoration in these children. Science 2016; 352: 1533

Eitan Israeli

**Capsule**

**Gut microbiota and undernutrition**

Poor nutrition during the early years of life can have severe consequences for subsequent skeletal, immunological, and intellectual development. Blanton et al. reviewed the evidence showing that undernutrition is not caused by food insecurity alone. Other factors range from the length of the breastfeeding period and the availability of milk oligosaccharides, enteropathogen exposure, and enteric dysfunction marked by villus atrophy and loss of gut barrier function. Unfortunately, nutritional restoration with or without antibiotic treatment may not be effective in the longer term. Differences in the succession of microbial establishment and maturity can explain much of family discordances in nutritional status. The evidence indicates that microbiota-directed therapeutics could be a promising route to nutritional restoration in these children. Science 2016; 352: 1533

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**Clues to cancer from an identity change**

The prostate and seminal vesicle have closely related developmental histories and both are regulated by the same androgenic hormones. A better understanding of the molecular mechanisms controlling the development of the two tissues could help explain why cancer arises frequently in the prostate but only rarely in seminal vesicles. Working with cell and mouse models, Dutta et al. showed that forced expression of a single gene, the homeobox gene \textit{NKX3.1}, causes seminal vesicle epithelium to differentiate into prostate. \textit{NKX3.1} regulates the expression of a gene program associated with prostate differentiation by interacting with the G9a histone methyltransferase. Disruption of this regulatory network probably contributes to prostate cancer development. Science 2016; 352: 157

Eitan Israeli

“In the kingdom of the blind, the one-eyed man is king”

Desiderius Erasmus (1466-1536), Dutch Renaissance humanist, Catholic priest, social critic, teacher, and theologian

“Friendship... is born at the moment when one man says to another ‘What! You too? I thought that no one but myself...’ ”

C.S. Lewis (1898-1963), British novelist, poet, academic, medievalist, literary critic, essayist, lay theologian, and Christian apologist. He held academic positions at both Oxford and Cambridge but is best known for his fictional work, especially \textit{The Chronicles of Narnia}