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In utero and early postnatal presentation of autoimmune lymphoproliferative syndrome in a family with a novel FAS mutation

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Autoimmune lymphoproliferative syndrome (ALPS; MIM 601859) is a congenital disease of defective T cell apoptosis and autoimmunity, most often caused by mutations in the FAS gene. The hematological manifestations of ALPS include chronic lymphadenopathy, splenomegaly, multilineage cytopenias secondary to sequestration and autoimmune destruction, and an increased risk of B cell lymphoma (1-3). Onset is typically early in life with a median age of 11.5 months (4). We report a family with a novel FAS mutation, in which the proband presented with onset of ALPS at 3 weeks of age and her brother in utero at 36 weeks gestation. To our knowledge these are among the earliest documented presentations of ALPS. Based on these cases, we now recommend obstetricians assess fetal spleen size by third trimester ultrasound in mothers with ALPS or a family history of ALPS, in addition to monitoring both mother and child for autoimmune hemolytic anemia and thrombocytopenia.

The proband, (NIH ALPS Family # 323.1) was born at 41 weeks gestation. She presented at age 3 weeks with pallor, vomiting, lethargy, jaundice, splenomegaly and lymphadenopathy. Prior to diagnosis, she developed worsening lymphadenopathy and massive splenomegaly. Lymph node biopsy showed few germinal centers and expansion of the paracortical zone with mature T-cells admixed with plasma cells and immunoblastic cells. Flow cytometry of peripheral blood showed 24% CD3+ T cells were CD4-/CD8- (Double Negative T cells; DNT) with increased alpha/beta population (60%). Fas mediated apoptosis assay showed cell kill of only 1.3% compared to normal control of 71.2%, consistent with ALPS. Given these findings, the clinical presentation and history, a diagnosis of ALPS was made as per the 2010 diagnostic criteria (5).

Sanger sequencing of the proband’s FAS gene (GenBank accession number M67454.1) in genomic DNA extracted from peripheral mononuclear blood cells revealed two variants: heterozygous c.761T>G , p.Val254Gly missense mutation and heterozygous c.642C>T single nucleotide polymorphism (SNP, rs2234978, average minor allele frequency T=0.236)(notation based on NM_000043). The c. 642C>T synonymous SNP is considered benign (6). The missense variant c.761T>G, to our knowledge, has not been reported previously but is located in the FAS death domain at an amino acid position that is biochemically conserved across species. Bioinformatics tools SIFT, SNP3D and PolyPhen predict c.761T>G is deleterious. Family studies revealed that the c.761T>G variant was paternally inherited and the c.642C>T SNP was maternally inherited.

The proband’s father was asymptomatic until 31 years of age (about a year after the proband’s birth), at which time he developed an unusual maculopapular rash. Skin biopsy showed pityriasis lichenoides et varioliformis acuta (PLEVA). The cause of this is unknown but it is considered to be a benign form of a T-cell lymphoproliferative disorder. He had an increased DNT population of 14% but interestingly, apoptosis testing showed no defect using Annexin V and 7-AAD assays. This is contrary to previous asymptomatic carriers who would normally still show apoptotic evidence of the gene defect (7-9). The mother had normal DNT cell numbers and apoptosis assay.
The proband's brother (NIH Patient family # 323.4) was diagnosed in-utero at 36 weeks gestation when a fetal ultrasound identified hepatosplenomegaly (see figure 1), mild cervical lymphadenopathy, cardiomegaly, polyhydramnios and anemia (based on middle cerebral artery flow). DNT CD3+ population was elevated at 21%. His FAS variants were identical to his sibling.

Reduced penetrance and variable phenotypic expression are seen in ALPS pedigrees, despite the affected individuals sharing the same FAS mutation (10, 11). Recent data suggests that both environmental factors and variants at other loci may be responsible for this (12). The novel genetic change we describe here lies in the intracellular region of the FAS gene, in exon 9, which encodes the death domain of the Fas protein. Mutations affecting the intracellular domain are associated with a higher penetrance than extracellular FAS mutations (8). As the father was not affected until later in life and the maternally inherited SNP appears to be benign (6), other factors clearly contributed to the severe phenotype of the proband and her sibling. Conceivably, the affected members of this family could have additional somatic changes to the FAS gene, as somatic changes in this gene have been implicated in the progression of ALPS (9). A cryptic deleterious maternally inherited FAS variant in the promoter or other noncoding region, for example, may be present but not detected by our sequencing. Alternatively, other mutations to proteins in the signaling cascade, such as FAS-ligand or FAS associated signaling proteins Procaspe 8/10 could contribute to the family phenotype. These possibilities warrant further genetic analyses, but are beyond the scope of this letter.

In summary, we present a novel death domain mutation in the FAS gene associated with in utero and early neonatal onset ALPS. It is an important differential to consider in antenatally and neonatally diagnosed splenomegaly. Significant morbidity and, possibly mortality, may be avoided if ALPS is included in an early differential. Given our experience, third trimester ultrasound is now suggested in mothers with ALPS or a family history of ALPS, to assess fetal spleen size. Both mother and child must be monitored for autoimmune hemolytic anemia and thrombocytopenia during pregnancy and postnatal period.
Authorship and Disclosures

JRH, MP and RS conceived this manuscript. JRH reviewed the literature, drafted the manuscript and coordinated the report. JRH, MP, EH, AF, RS, KR participated in the families management. EH, AF, BB, JN, JD were involved in the flow cytometry and mutation analysis for the family. KR and RS have acted as the senior clinicians and authors. Finally, all authors were intimately involved in the preparation and editing of the final manuscript.

References

Figure 1. Splenomegaly with span 7cm extending into the pelvis