We describe an association between congenital patent ductus venosus and hyper immunoglobulin E syndrome in a pair of siblings. The possibility that this is a separate entity or a genetically linked association is discussed. (J Pediatr 2007;150:210-2)

Congenital portosystemic shunts (PSS) are rare malformations involving the vasculature leading into and out of the liver. The clinical consequences of a shunt from the portal vein to the systemic veins are portal hypertension and hepatic encephalopathy. Congenital shunts have been occasionally associated with other malformations that include heterotaxia, Goldenhar’s syndrome, biliary atresia, mental retardation, and genitourinary malformations.

Congenital patent ductus venosus (PDV) is a rare disorder involving a shunt from the fetal umbilical vein to the inferior vena cava. Spontaneous closure of the ductus venosus is the rule in normal infancy, usually immediately or within the first few weeks after birth. There is no evidence linking hypercoagulable states and the development of PDV at present. Familial congenital PDV has been reported only 3 times to date, in 2 case reports involving 2 sets of 3 siblings each and in 1 set of twins without underlying diseases or syndromes.

Hyper immunoglobulin E (IgE) syndrome (HIES) is a rare primary immunodeficiency syndrome characterized by recurrent staphylococcal infections, pneumonia, eczema, prominent jaw with coarse facies, and markedly elevated serum IgE levels, usually >2000 IU/L. Most cases are sporadic; however, families with autosomal dominant (AD) and autosomal recessive modes of inheritance have been described.

An association between HIES and vascular liver anomalies has not been described. We present 2 siblings with identical portosystemic hepatic shunt–PDV and HIES and discuss whether these 2 entities are separate or share a common genetic pathway.

CASE REPORT

Patient 1

A 5-year-old male previously diagnosed with HIES was admitted to our hospital because of a staphylococcal hepatic abscess and peritonitis. The diagnosis of HIES was established on the basis of clinical features, including recurrent skin abscesses, eczemas, recurrent oral thrush, prominent teeth, and upper jaw with coarse facies. Immunologic workup revealed IgE levels usually above 4000 units/mL (normal < 230). Other immunoglobulin levels were within the normal range.

Absolute eosinophil counts were in excess of 2000/mL (normal < 800). Neutrophil function testing did not detect chemotactic or bacteriocidic abnormalities; superoxide formation was normal. There was no response to a Candida sp. skin test, and the response to the diphteria tetanus (DT) skin test was normal. Lymphocytic subpopulation and response to mitogen was normal.

Past history revealed 4 normal siblings and a younger sister described below as patient 2. The patient’s parents are of non-consanguineous Arab origin. His father has a
hypereosinophilic syndrome with recurrent episodes of cellulitis and cutaneous fungal infection. The father’s abdominal ultrasound scan demonstrated a normal liver with normal liver vasculature.

Physical examination revealed microcephaly, prominent teeth and upper jaw as mentioned, and prominent ears. The liver was not palpable; the spleen was palpated 2 cm below the costal margin. A neurologic and developmental assessment revealed that the boy had mild mental retardation with attention deficit disorder with hyperactivity. No neurologic focal findings or asterixis were demonstrated.

Relevant laboratory test results include alanine amino transferase of 39 units/L (norm < 41), aspartate aminotransferase of 52 units/L (norm < 38), mildly increased alkaline phosphatase of 744 units/L (norm 145-320), and albumin of 4.1 g/dL (norm 3.8-5.4). The ammonia was constantly elevated above 200 units/L (normal range 9-33 U/L). The result of echocardiography was interpreted as normal. A liver biopsy specimen from an area of nodularity disclosed congestion without evidence of inflammation and without fibrosis. The electroencephalography result was normal. During the post-laparotomy assessment, contrast-enhanced abdominal computerized tomography and ultrasound Doppler examination demonstrated a shunt from the left portal vein through a PDV to the infradiaphragmatic inferior vena cava. The right portal vein was hypoplastic (Figure).

**Patient 2**

Briefly, patient 2 is the 9-year-old sister of patient 1. Her history was unremarkable except for a periodontal abscess and Thalassemia minor. Because of an enlarged liver palpated 2 cm below costal margins and palpable spleen (edge) on physical examination and a brother known to have congenital PDV and HIES, she was evaluated for the latter 2. Her facial characteristics show prominent teeth and upper jaw very similar to her brother’s. Neurologic and developmental assessment was normal. She, like her sibling, had never had cyanosis.

Her blood test revealed elevated ammonia of 130 units/L, normal alanine amino transferase, aspartate aminotransferase, and alkaline phosphatase. Her total IgE is 1896 units/L, normal alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. The absolute eosinophil count was 390/mL. Liver ultrasonography with Doppler scanning and contrast enhanced abdominal computerized tomography demonstrated similar findings to those of her brother—a large shunt through a PDV with a hypoplastic right portal vein. Neither patient had evidence of a hypercoagulable state by laboratory evaluation. Cytogenetic analysis was performed on peripheral blood lymphocytes of patient 1 and patient 2 by use of G-bands by trypsin using Giemsa (GTG) banding techniques. No major deletion or translocation of the 4q region did was detected.

**DISCUSSION**

The rarity of coexisting PDV and HIES in 2 siblings and the fact that their father also has elevated IgE with eosinophilia suggests that this is not a coincidence. This association raises several possibilities: a single genetic defect leading to both syndromes, 2 different syndromes occurring in the same individuals, or that the presence of 1 syndrome might lead to the other.

PDV is considered a rare sporadic phenomenon. The only prior evidence for a genetic cause as a possible cause comes from 2 previous reports, each containing 3 siblings (described in the introduction). A second clue is that congenital PSS is not rare in dogs, suggesting that a genetic mutation may cause PSS.7 The fact that 2 siblings share the same shunt without evidence of a hypercoagulable state lends credence to a genetic hypothesis for PDV.

HIES on the other hand, has been clearly linked to an underlying genetically inherited abnormality in some patients. Grimbacher et al8 described 19 kindreds with 57 individuals affected with HIES in an AD mode of inheritance. In some of the patients they found linkage to 4q21-4q21.1 locus. A candidate gene is not known. The 2 siblings and their father could fit a hyper IgE–associated AD trait.

One possible explanation of the association we have described is that this is a previously unpublished genetic syndrome. Another possible connection between these 2 rare entities could be 2 rare genetic traits in the same family. In highly consanguineous populations, such as exist in the Middle East, it is not uncommon to find 2 genetic traits in the same family.

Another possible genetic cause may involve a mutation or deletion to a common locus involving more than genes. Regulation of fetal vasculature and closure of intrauterine shunts is often mediated by prostaglandins. The prostaglandin D2 synthase (the hematopoietic type among the 3 isoenzymes) is located downstream from the hyper IgE locus on the 4q21-q22 locus (omim 602598). Prostaglandin D2 is a cofactor in the development regulation of the fetal circulation in animal models.9-12
We did not find a translocation or a major deletion in this location by chromosomal analysis of the 2 siblings and the father. Although a mutation scenario is appealing, we do not have any evidence that mutation in the PGD synthase is related to PDV. Lastly, presence of an underlying immunologic deficiency may predispose individuals toward dysregulation of the fetal vasculature. Although mast cells may secrete vascular endothelial growth factor in response to IgE, there is no prior evidence to date to suggest that situations with abnormal IgE affect the fetal circulation.13

In conclusion, we have described an association between PDV and HIES in 2 siblings. This association may be a novel syndrome. The finding of a fourth set of siblings with PDV strongly suggests that genetic mutations may be responsible for some cases of this entity.

REFERENCES