Eur J Pediatr (2010) 169:315–318
DOI 10.1007/s00431-009-1030-0

ORIGINAL PAPER

Familial isolated congenital asplenia: case report and literature review

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Received: 5 April 2009 / Accepted: 30 June 2009 / Published online: 19 July 2009

Abstract Congenital asplenia is a rare life-threatening condition, often presenting with pneumococcal sepsis. It may arise as part of situs abnormalities or result from an unrelated specific defect of spleen development. The mode of inheritance is usually autosomal dominant, though sporadic cases are also reported. In affected individuals, the use of appropriate antibiotic prophylaxis and immunisations could save lives. In our report, we describe a family of three siblings with isolated congenital asplenia and unaffected parents, suggestive of recessive inheritance. The diagnosis in the proband was made post mortem following overwhelming pneumococcal sepsis. We also review the literature and compare the eight families previously reported with congenital isolated asplenia

Keywords Familial asplenia · Howell–Jolly bodies · Isolated congenital asplenia · Pneumococcal sepsis

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Abbreviations
HJB Howell–Jolly bodies
US Ultrasound

Introduction

Splenic phagocytes play an important role in removal of complement opsonised pneumococci from the blood, a process which is enhanced by the presence of specific antibody against the polysaccharide capsule of the organism. These immunological observations are supported by clinical experience in which deficiency of specific antibody or hyposplenism led to an increase in the risk of pneumococcal disease [2, 9]. Asplenia can be functional as in sickle cell anaemia, acquired after trauma or surgery, or congenital (see Table 1). Congenital asplenia often occurs in the context of a recognised malformation syndrome: the Ivemark syndrome, also called asplenia syndrome (OMIM 208530) [12, 20]. In this syndrome, malformations arise as lateralisation defects of organs in the thorax and the abdomen, now classified as situs abnormalities or heterotaxia syndromes with or without cardiac abnormalities, which are clinically and genetically heterogeneous conditions [1]. Different modes of inheritance have been reported for these syndromes, mostly autosomal recessive [6, 28], exceptionally autosomal dominant [1] or X-linked [5]. Two human genes, connexin 43 [4] and ZIC3 [14], have been shown to be involved in heterotaxia syndromes. No human genes have been identified in isolated congenital asplenia. In this paper, we report on a family where the index case was diagnosed with congenital isolated asplenia on post-mortem examination. Further investigations in the first-degree relatives showed that two

Table 1 Causes of asplenia

1. Congenital
Genetic disorders (heterotaxy syndrome)
Exposure to environmental factors during gestation [31]
2. Acquired
After splenectomy in patients with ITP, thalassemia, spherocytosis and after splenic rupture from trauma or tumour. Autosplenectomy in sickle cell disease

of the siblings were affected but a third sibling and the parents were unaffected.

Case report

A previously healthy 8-month-old female infant presented with a 4-h history of fever, shallow breathing, lethargy and vomiting. On examination, she was found to be in septic shock with a pulse of 200–210 per minute and mean blood pressure of 59 mmHg. Peripheral areas were cold with a capillary refill time of 8 s. The rectal temperature was 38.6°C. There were signs of respiratory distress with subcostal, intercostal and supra sternal retractions and tracheal respiratory rate was 40 breaths per minute. She was in 100% oxygen and her saturations remained between 80% and 90% in 15 l/min of oxygen through face mask. She had fluctuating level of consciousness with no focal neurological deficit.

Initial laboratory investigations revealed: haemoglobin 12.3 g/dl; white cell count 4.3×10^9/l (neutrophils 1.1 and lymphocytes 3.15×10^9/l); platelet count of 367×10^9/l. Her renal function test, liver function test, bone profile and C-reactive protein were within normal ranges for the age. A mixed respiratory and metabolic acidosis was present (pH 7.15, pCO_2 13.2, bicarbonate 13.5, base deficit of −11). The initial chest radiograph was normal but pulmonary oedema developed during resuscitation. Despite respiratory support, volume replacement therapy and inotropic support the infant died following two cardiopulmonary arrests.

Pneumococcal PCR performed on an admission blood sample was positive but blood cultures were negative. Post-mortem examination revealed an absent spleen, leading to

Table 2 Reported cases of familial congenital isolated asplenia

Reference	Number of cases	Case	Age at diagnosis/ gender	Clinical events	Outcome
	1	Proband	8 months/female	Pneumococcal sepsis	Died
		Brother	2 years/male	Asymptomatic	Alive
		Brother	5 years/male	Asymptomatic	Alive
[17]	2	Proband	4 months/male	Pneumococcal sepsis, HJB	Survived, limb amputation
		Sister	21 months/female	Undocumented sepsis, HJB	Died
[23]	3	Proband	10 months/female	H. Influenza meningitis	Died
		Sister	3 years/female	H. Influenza septicaemia, HJB	Survived
		Brother	4.5 years/male	Repeated pneumococcal meningitis, HJB	Survived
[22]	4	Proband	7 months/female	Undocumented sepsis	Died (22)
		Sister	1 year/female	Undocumented sepsis, Gastrointestinal malformation	Died
[10]	5	Proband	2 years/female	Undocumented overwhelming severe sepsis	Survived, limbs amputations
		Sister	2 months/female	Asymptomatic, HJB	Alive
[13]	6	Proband	6 months/female	Pneumococcal sepsis	Died
		Mother	Unknown/female	Asymptomatic	Alive
		Brother	3.5 years/male	Pneumococcal sepsis	Died
[30]	7	Proband	11 months/female	Repeated pneumococcal meningitis, HJB	Died
		Father	45 years/male	Pneumococcal meningitis, HJB	Alive
[24]	8	Proband	7 months/male	Repeated otitis, HJB	Alive
		Father	25 years/male	HJB, thrombocytosis	Alive
[24]	9	Proband	12 years/male	Pneumococcal sepsis	Died
		Father	Unknown/male	Asymptomatic	Alive

investigation of the other family members. Two of the siblings were found to be affected (Howell–Jolly bodies present on the blood film and absent spleen on ultrasound) but a third sibling and the parents were unaffected.

Discussion

Congenital isolated asplenia may be a minor form of situs abnormality or a separate entity due to a specific defect of spleen development. A total of nine families with congenital isolated asplenia have been described since the first report of Myerson and Koelle in 1956 [25]. Twenty one cases have been identified among these nine published families, and the clinical details of the reported cases are summarised in Table 2. In ten cases, the first sign of congenital isolated asplenia was severe or overwhelming sepsis, one presented with repeated otitis media and four cases presented with meningitis. There were six asymptomatic cases. Of the two affected adults reported (families 7 and 8), neither presented with severe sepsis in infancy. This outlines the wide inter- and intra-familial variability.

Katcher et al. [22] described a patient with isolated congenital asplenia and her sister (family 4) who had congenital asplenia associated with a gastrointestinal malformation (imperfectly rotated large intestine, liver with the right and the left lobes the same size and gallbladder arising from the right lobe). This latter report favours a situs abnormality. In all other reports, the asplenia was isolated.

When asplenia occurs as part of heterotaxy syndromes, it is often identified before it becomes symptomatic due to the presence of other congenital anomalies. Appropriate prophylaxis may then be instituted in order to prevent overwhelming sepsis. However, in the case of congenital isolated asplenia, there are no other physical clues to the diagnosis and pneumococcal sepsis may be the first sign of the disease [3, 18, 19, 29]. Thrombocytosis is a common feature of myeloproliferative disorders but may also result from various conditions including chronic iron deficiency, hemorrhage, chronic inflammation and splenectomy. Chanet V et al. [7] report two cases of secondary thrombocytosis caused by isolated and congenital asplenia, mimicking essential thrombocythemia [7, 27]. The diagnosis is often made on post-mortem examination [11].

In the nine families reported, families 6–9 show an autosomal dominant inheritance, with a parent and offspring being affected. In families 2, 4, and 5, it is difficult to assess the pattern of inheritance as the parents were not investigated. Hence, among the nine families reported, there is only one family (family 3), other than our own, which shows autosomal recessive inheritance.

A small proportion of patients with heterotaxy syndromes associated with polyasplenia (Ivemark syndrome) have been shown to be compound heterozygotes for mutations in the connexion 43 gene, indicating an autosomal recessive inheritance (4). Also, some families with an X-linked form of heterotaxy syndrome have been shown to have mutations in the ZIC3 gene (14). However, no human genes have been implicated in the pathogenesis of isolated asplenia so far. Roberts et al. [26] found isolated asplenia in mice with homozygous deficiency of the HOX11 gene. Kanzler and Dear [32] demonstrated in mice that although the HOX11 gene was not crucial in the early formation of the spleen primordium, it was essential for the subsequent differentiation of spleen precursor cells, the failure of which led to asplenia. We tested our family for mutations in the TLX1 gene, which is the human orthologue of the mouse HOX11 gene and could not identify any mutations.

The diagnosis of congenital isolated asplenia following presentation with pneumococcal disease should be considered, particularly in the event of overwhelming sepsis, given the importance of identifying other family members with the condition. Dyke [8] reported 5 cases of congenital asplenia associated with adrenal haemorrhage in 4 cases with overwhelming sepsis with Haemophilus influenza and death within 24 hrs. Gill [16] and Kanthan [21] reported an autopsy finding of pneumococcemia and acute bilateral adrenal haemorrhage with asplenia in a 4 yr old with sudden unexpected death. The diagnosis of functional asplenia in the context of pneumococcal sepsis can be confirmed by identification of Howell–Jolly bodies on a blood film or surface pits in the erythrocyte membrane using phase contrast microscopy and the absence of the spleen noted on ultrasound examination of the abdomen [15]. In the case of congenital isolated asplenia, use of appropriate prophylaxis with penicillin and ensuring active immunisation with pneumococcal and Hib vaccines could prevent overwhelming sepsis and save the lives of affected children.

Conclusion

It is already known that congenital isolated asplenia is a rare condition, which is heterogeneous in its presentation. It also appears to be heterogeneous in its inheritance as, although the majority of families reported show autosomal dominant inheritance, there are at least two families in the literature now which demonstrate autosomal recessive inheritance. As no human genes have been identified as being causative in isolated asplenia as yet, abdominal ultrasound and blood film for Howell–Jolly bodies are the important investigations to perform in the first-degree relatives of affected individuals to diagnose asplenia.

Conflict of interest None

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