Isolated Congenital Asplenia: A French Nationwide Retrospective Survey of 20 Cases

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Objective To better describe the natural history, mode of inheritance, and the epidemiological and clinical features of isolated congenital asplenia, a rare and poorly understood primary immunodeficiency.

Study design A French national retrospective survey was conducted in hospital pediatric departments. A definitive diagnosis of ICA was based on the presence of Howell-Jolly bodies, a lack of detectable spleen, and no detectable cardiovascular malformation.

Results The study included 20 patients (12 males and 8 females) from 10 kindreds neither related to each other nor consanguineous. The diagnosis of ICA was certain in 13 cases (65%) and probable in 7 cases (35%). Ten index cases led to diagnosis of 10 additional cases in relatives. Five cases were sporadic and 15 were familial, suggesting autosomal dominant inheritance. Median age was 12 months at first infection (range, 2-516 months), 11 months at diagnosis of asplenia (range, 0-510 months), and 9.9 years at last follow-up (range, 0.7-52 years). Fifteen patients sustained 18 episodes of invasive bacterial infection, caused mainly by *Streptococcus pneumoniae* (61%). Outcomes were poor, with 9 patients (45%) dying from fulminant infection.

Conclusions ICA is more common than was previously thought, with an autosomal dominant inheritance in at least some kindreds. Relatives of cases of ICA should be evaluated for ICA, as should children and young adults with invasive infection. *(J Pediatr 2011;158:142-8)*.

Congenital asplenia is often associated with complex visceral defects, as part of the so-called "visceroatrial" heterotaxy syndromes.[1,2] Perhaps the best known among these heterotaxy syndromes is the asplenia/polysplenia syndrome (AS; OMIM #208530), which was fully documented by Ivemark in 1955.[1] Patients suffering from this syndrome have a complete absence of splenic tissue, marked hyposplenia (right-sided isomerism), or in some cases polysplenia (left-sided isomerism). They also suffer from various anomalies of the heart and great vessels. The majority of cases are sporadic, although familial cases have been described. Heterotaxy syndromes can be autosomal recessive (AR),[3] autosomal dominant (AD),[4] or X-linked recessive (XL).[5] Mutations have been identified in various genes controlling left-right laterality.[6-8] There is variable penetrance and phenotypic variability in the familial forms of heterotaxy, the incidence of which is about 1/10 000 to 1/40 000 live births.[9] Although life-threatening infections have been reported in affected individuals, the main causes of death are related to cardiac complications, especially in the first year of life.[2,10-14] Some cases of AS are diagnosed late in life, however.[15]

In contrast, patients with isolated congenital asplenia (ICA; OMIM#271400) lack other developmental anomalies, particularly those of the cardiovascular system. Since the first case report by Myerson and Koelle in 1956,[16] ICA has been thought to be exceedingly rare; no large series of patients has been reported.

AD	Autosomal dominant
AR	Autosomal recessive
AS	Asplenia syndrome
CT	Computed tomography
HJB	Howell-Jolly bodies
ICA	Isolated congenital asplenia
US	Ultrasound
XL	X-linked recessive

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Only case reports have been recorded in the medical literature.[13,14,16-37] Of the 50 reported cases of ICA recorded in the medical literature,[13,14,16-37] 24 were sporadic and 26 were familial, belonging to 11 unrelated families (a total of 31 families worldwide). Thirty-three of the cases were in children and 13 were in adults; age was not available for 4 cases. The sex distribution was 22 males, 21 females, and 7 not reported. Among the 11 multiplex families reported, the transmission of ICA was suggestive of autosomal dominance in 6 families[19,22,30,34,38] and was either AD or AR in the remaining 5 families.[24,28,29] Consanguinity was noted in 2 multiplex families.[28,29] The ethnic origin was reported in 3 multiplex families, one each of Dutch-French, French, and white Australian descent.

At least 45 episodes of severe bacterial infection occurred in the 50 reported cases of ICA. Up to 20 of these 50 patients died of overwhelming bacterial infection. No noninfected patient died. Conversely, 13 patients survived severe infection. Seven patients experienced several episodes of invasive bacterial infections, all caused by *Streptococcus pneumoniae.* Multiple deaths in the same kindred were reported in 2 unrelated families.[28,34] Necropsy performed in 11 patients showed no cardiac abnormalities and a vestigial spleen.

Our understanding of the epidemiologic and clinical features of ICA, already somewhat clarified by the 50 reported cases, would gain much more from the description of a larger series of patients. Consequently, we undertook a retrospective multicenter study of ICA in France.

Methods

Between January 2002 and January 2003, a clinical questionnaire aimed at retrospectively recording cases of ICA in France was sent to all members of 4 French Pediatric Societies: the Pediatric Intensive Care and Emergency Group, the French Pediatric Intensive Care Society, the French Pediatric Infectious Diseases Group, and the Pediatric Immunology and Hematology Society. The Pediatric Cardiology Society was not solicited. Of 443 solicited clinicians, 294 (66%) responded to the survey by January 2003, the study's endpoint. All clinical, radiologic, and microbiologic findings were reviewed by V.M.-C. or N.M., and all blood smears were reviewed by F.V. Familial screening for ICA was performed by physical examination, abdominal ultrasound (US), and examination for Howell-Jolly bodies (HJB) in peripheral blood smears. Patients' and family members' cardiovascular systems were clinically reviewed and explored using echocardiography by D.B. This retrospective study was undertaken in accordance with French regulations, with the informed consent of each patient and family.

The study was approved by the local Ethics Board in Necker-Enfants malades Hospital, Paris, France. The diagnosis of ICA was considered certain when the presence of HJB was documented on a peripheral blood smear and the absence of splenic tissue was documented by abdominal US, computed tomography (CT) scan, magnetic resonance imaging, or classical isotopic Tc^{99m} splenic scintigraphy. Normal heart and great vessels were documented by US examination. ICA also could be defined as certain based on necropsy findings. ICA was considered probable in patients who had a severe bacterial invasive infection and in whom HJB were detected but no information on spleen morphology was available, or in whom blood smears were not detected but necropsy established a missing spleen. ICA was defined as possible when a familial history of ICA and a personal history of invasive bacterial infection were reported but paraclinical data were unavailable. Echocardiography and electrocardiography were performed to identify situs anomalies and cardiac defects, with particular attention given to pulmonary and systemic venous connections. In each family, the index case was the first individual diagnosed with ICA. Serious invasive infection was defined as a life-threatening infection (meningitis, septicemia, or purpura fulminans).

Statistical Analysis

Clinical data were individually analyzed and then compared with available published data in the international literature. Survival analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina). Continuous variables were presented with medians or means. Survival analyses were performed using the Kaplan-Meier method, with a log-rank significance defined as $P < .05$.

Results

Characteristics of Probands and Affected Relatives

Ten index cases (5 males and 5 females) led to the identification of ICA in a total of 20 patients (12 males and 8 females) from 10 unrelated kindreds (**Figure 1**). These individuals were born between 1957 and 2006, during which approximately 39.2 million births were recorded in France. Thus the prevalence of ICA can be estimated as at least 0.51 per million births. All probands were diagnosed in childhood, at a median age of 11 months. The screening of members from the 10 families led to the identification of 10 other patients with ICA in 5 kindreds. These 10 patients included 5 with certain ICA and 5 with possible ICA. One patient who died after a second severe pneumococcal infection was excluded due to a normal spleen on US examination.

Affected relatives were diagnosed at a median age of 11 months (range, 0 months to 42.5 years). There were 5 sporadic cases and 15 familial cases, belonging to 5 multiplex kindreds (3 with 2 affected members, 1 with 4 affected members, and 1 with 6 affected members). Seven families were Caucasian, originating from various regions of France, including Brittany (n = 2), Normandy (n = 2), Picardy (n = 1), and central and northern France (n = 2). Family D originated from Reunion Island (Tamoul father and metropolitan French Caucasian mother), family E originated from Congo-Brazzaville (central Africa), and family I originated from France (metropolitan French Caucasian father) and Cameroon in western Africa (mother). None of the parents

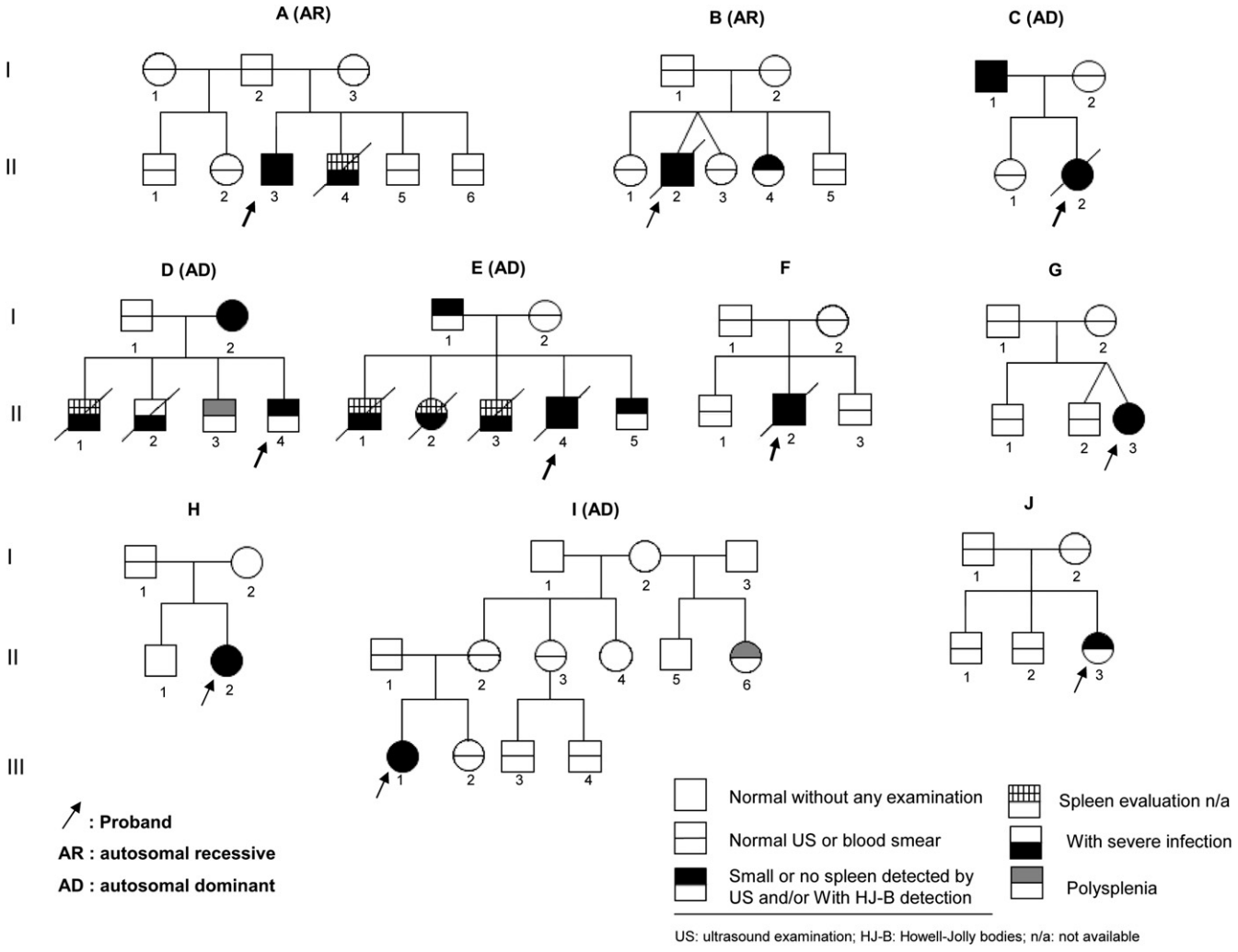

Figure 1. Pedigrees of the 10 families with ICA.

were consanguineous, and none of the 10 families were related to each other.

Biological, Radiologic, and Necropsy Findings

HJBs were detected on blood smears in all of the 13 patients tested. Standard blood counts found thrombocytosis in 4 cases, with a median platelet count of 638 000/mm^3 (range, 468-740). Immunologic evaluation revealed normal levels of IgG, IgA, and IgM; lymphocyte subpopulations; and complements C3 and C4 (data not shown). Following documented infection with *S pneumoniae*, antipneumococcal plasma antibodies were measured in 4 patients and found to be above the detection threshold at a protective titer in 2 patients. Four patients had detectable antipneumoccocal IgG after receiving a pneumococcal vaccination; of these 4 patients, 2 received a combination of the 23-valent polysaccharide vaccine (P23) and the 7-valent conjugate vaccine, 1 patient received only the former, and 1 patient received only the latter. Abdominal US performed in 10 patients found a total lack of a spleen in 8 and a rudimentary spleen in 2 with normal Doppler examination (proband E-II-4's spleen measured 1.86 × 0.5 cm; a measurement was unavailable for the other patient). HJB were detected in both patients. Neither patient sustained any severe infection while on antibiotic prophylaxis. Six patients had an abdominal CT scan (4 patients) and/or classical isotopic Tc^{99m} splenic scintigraphy (5 patients), the results of which were correlated with the US findings. Autopsies were performed in 2 cases (Table), leading to the confirmation of isolated spleen atrophy (1 × 0.5 cm in B-II-2 and 2 × 1.5 × 0.5 cm in D-II-4). Cardiovascular examination was performed in 11 patients, including 8 probands (6 of whom are alive), and 14 family members; members of 3 families were not studied. None of the patients with ICA had any clinical or US signs of heterotaxia, strongly suggesting that ICA and AS are two clearly separate entities, at least clinically speaking. Apparently there is no detectable clinical continuum between AS and ICA, despite the clinical heterogeneity of the AS itself, which encompasses variable cardiovascular anomalies, ranging from severe defects during the neonatal period to malformations manifesting in childhood.

Table. Characteristics of probands and their relatives with isolated asplenia

Patient	Sex	Infections	Age at first infection or at diagnosis	Identification	HJB	Documented asplenia	Outcome	ICA status
A-II-3	Proband/M	Otitis and meningitis	10 months	*S pneumoniae* 23F	Yes	Hyposplenia (US/Doppler, CT scan, scintigraphy)		Certain
		Purpura fulminans	11 months	*S pneumoniae*				
		Purpura fulminans	19 months	*S pneumoniae*			A/W	
A-II-4	Brother/M	Purpura fulminans	10 months	NA	ND	NA	Death in 12 hours	Possible
B-II-2*	Proband/M	Meningitis and purpura fulminans	22 months	*S pneumoniae*	ND	Yes (necropsy)	Death in 12 hours	Certain
B-II-4	Sister/F	No infection	0	-	Yes	Yes (US, scintigraphy)	Alive, osteosarcoma (12 years)	Certain
C-I-1	Father/M	Meningitis	43 years	*S pneumoniae*	Yes	Yes (US, CT scan)	A/W	Certain
C-II-2†	Proband/F	Otitis and meningitis	6 months	*S pneumoniae*				Probable
		Otitis, meningitis, and purpura fulminans	11 months	*S pneumoniae* 23F	Yes	NA	Death in 10 hours	
D-I-2	Mother/F	Septicemia	20 years	*S pneumoniae*	Yes	Yes (US)	A/W	Certain
D-II-1	Brother/M	Purpura fulminans	36 months	*S pneumoniae*	NA	NA	Death in 6 hours	Possible
D-II-4‡	Proband/M	No infection	12 months	-	Yes	Marked hyposplenia (US/Doppler)	A/W	Certain
E-I-1	Father/M	No infection	35 years	-	Yes	Yes (US)	A/W	Certain
E-II-1	Brother/M	Septicemia	12 months	NA	NA	NA	Death	Possible
E-II-2	Sister/F	Septicemia	8 months	NA	NA	NA	Death	Possible
E-II-3	Brother/M	Septicemia	8 months	NA	NA	NA	Death	Possible
E-II-4	Proband/M	Purpura fulminans	23 months	*Streptococcus α hemolyticus*	NA	Yes (necropsy)	Death in 29 hours	Certain
E-II-5	Brother/M	No infection	2 months	-	Yes	Yes (US, CT scan, scintigraphy)	Alive, autism	Certain
F-II-2	Proband/M	Purpura fulminans	10 months	*S pneumoniae*	Yes	NA	Death in 20 hours	Probable
G-II-3	Proband/F	Purpura fulminans	6 months	NA	Yes	Yes (US, CT scan, scintigraphy)	A/W	Certain
H-II-2	Proband/F	Otitis and septicemia	20 months	NA	Yes	Yes (US, CT scan, scintigraphy)	A/W	Certain
I-III-1§	Proband/F	Purpura fulminans	12 months	*S pneumoniae*	Yes	Yes (US)	A/W	Certain
J-II-3	Proband/F	No infection	7 months	-	Yes	Yes (US)	A/W	Certain

A/W, alive and well; *NA*, not available; *ND*, not determined.
*Case reported by Ferlicot et al.[20]
†Case reported by Gilbert et al.[22]
‡The proband has a brother with a normal-sized spleen but a severe infectious phenotype and another with a bilobar spleen but no infectious phenotype.
§A half-sister of the mother's proband has a polysplenia.

Severe Infections in Probands and Relatives

Fifteen patients (75%) had a positive history of invasive bacterial infection. The median age at first infection was 12 months. All but 2 probands presented with an invasive bacterial infection. Two probands had more than one episode of invasive bacterial infection, both caused by *S pneumoniae*. No other type of severe infection was noted. Median age at onset of infection in symptomatic probands was 12 months. For 3 symptomatic probands (from families C, D, and E), the diagnosis of ICA was preceded by an invasive bacterial infection in at least one other family member. Seven of 10 relatives with certain or possible ICA were symptomatic. These individuals were found in 4 kindreds (families A, C, D, and E). Two of these 7 patients had a certain ICA (C-I-1 and D-I-2) and are alive and well without antibiotic prophylaxis or immunizations. The remaining 5 died of invasive bacterial infection. Overall, the 15 patients with infection sustained 18 episodes of severe bacterial infection affecting the central nervous system (meningitis) and/or the bloodstream (septicemia and purpura fulminans). Among these episodes were 10 episodes of purpura fulminans in 9 patients, all but 2 of which were caused by *S pneumoniae*. Five episodes of meningitis occurred in 4 patients, all caused by *S pneumoniae*. Four episodes of septicemia occurred in 4 patients, caused by *S pneumoniae* in 1 and by an undetermined bacterium in 3. Four episodes of acute otitis media were associated with an invasive bacterial infection in 4 different patients, caused by *S pneumoniae* in 3 cases (2 of the 23F serotype) and by an undetermined bacterium in 1 case. Overall, microbiologic data were documented for 12 episodes (67%). *S pneumoniae* was documented in 11 different invasive bacterial infections (61%), 2 of which were of the 23F serotype (18%). Six episodes of invasive bacterial infection were undocumented. None of the patients with ICA who died of severe pneumococcal infection had received antibiotic prophylaxis or antipneumococcal vaccine before the infectious episode. The patients with invasive bacterial infection had a total of 162 years of follow-up without prophylaxis and 49 years of follow-up with prophylaxis. There was at least one episode of severe infection in 9% of the years without prophylaxis and in 2% of the years with prophylaxis, a non–statistically significant difference.

Screening of Subjects with Asymptomatic ICA

The screening of 58 members (including 20 patients with ICA and 38 relatives) in these 10 families led to the diagnosis of 5

patients before occurrence of invasive infection. These included 1 adult (E-I-1) and 4 children. Among these were 2 probands (D-II-4 and J-II-3) diagnosed at 12 and 7 months, respectively. In the latter, diagnosis was made during an US examination performed for evaluation of intussusceptions workup. In the former, screening was done because of a positive history of invasive bacterial infection in the patient's brothers and mother. Interestingly, proband D-II-4 had marked hyposplenia, and his asymptomatic brother (D-II-3) had a bilobed spleen with a normal Doppler US examination and no HJB on repeated blood smear examinations. This family also included 2 older brothers (D-II-1 and D-II-2) who had died of fulminant invasive pneumococcal infection, one of whom had a normal spleen on an US examination (not Doppler). Unfortunately, autopsy was not performed in these 2 patients. In family I, screening led to the diagnosis of polysplenia in the asymptomatic half-sister of the proband's mother, who had no HJB on repeated blood smear examinations. Diagnosis was made at birth in one patient (B-II-4) due to the patient's brother's history of invasive bacterial infection. Screening of family E led to the diagnosis of ICA in 2 related asymptomatic patients (E-II-5 and his father, E-I-1). Following the diagnosis, we recommended immunization against *S pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*; daily antimicrobial prophylaxis without penicillin; and aggressive parenteral antibiotic treatment in the case of acute febrile illness. Patient D-II-4 discontinued antibiotics at 8 years after diagnosis, and patient E-1-1 refused antibiotic therapy.

Survival and Outcome

Nine of the 20 patients died (45%), at a median age of 12 months (range, 8-36.8 months). Overwhelming septicemia was the cause of death in all 9 patients. Nine of the 15 patients (60%) who experienced a severe infection died (**Figure 2**; available at www.jpeds.com). Four of the 8 symptomatic probands (50%) died of overwhelming sepsis. Among the surviving probands, 1 patient had 3 episodes of invasive pneumococcal infection (at age 10, 11, and 19 months), leading to a diagnosis of ICA. The other 3 patients (G-II-2 current age 10 years; H-II-2, age 26 years; and I-III-1, age 8 years) each had one episode of invasive bacterial infection. Among the 7 symptomatic relatives, death was caused by a severe invasive infection in 5 children (71%) at a median age of 11 months (range, 8-36 months). Patient D-II-1 experienced 2 severe bacterial infections caused by *S pneumoniae* of serotype 23F. The 2 ICA symptomatic adult relatives (C-I-1 and D-I-2) each had a pneumococcal invasive bacterial infection before the diagnosis of ICA was made (at age 43 and 20 years, respectively), with a favorable outcome. Nonetheless, survival probability according to age at first invasive bacterial infection was the same in patients age $\leq$2 years compared with others. Immunization, daily oral antibiotic prophylaxis, and urgent parenteral antibiotic therapy in the event of high fever were recommended for all relatives with ICA. Three asymptomatic relatives remained free of severe bacterial infection under appropriate recommendations; however, B-II-4 eventually developed an osteosarcoma at age 12, and E-II-5 developed a mental disease similar to autism. Median age at last follow-up was 9.9 years (range, 0.7-52 years).

Discussion

Our report of 20 patients with ICA from 10 kindreds in a national multicenter study in France adds to the previously published 50 case reports and small single-center series among 31 families. The incidence of ICA has been estimated based solely on postmortem series. Kanthan et al[27] reviewed 293 pediatric autopsies after sudden unexpected death and identified 4 cases of asplenia, including 3 cases of AS and 1 case of ICA. In our series, the prevalence of ICA can be roughly estimated as at least 0.51 per million births over a 50-year period in France. Given the rate of fatality from a first infection in patients with ICA, along with the positive family history when index cases are interviewed and relatives are screened, some children likely were undiagnosed and thus not recorded later. Therefore, it should be emphasized that this prevalence is a minimal estimation, given the limitations of a retrospective study, especially for a disease characterized by sudden death by infectious disease with no preexisting warning signs.

In our series, the 14 invasive pneumococcal diseases occurred during the 25-year period 1979-2004. Nine of these cases occurred between 1988 and 2002. During this period, an estimated 6510 invasive pneumococcal diseases occurred in French children aged <24 months. Between 1991 and 2007, a total of 92 033 episodes of severe pneumococcal infections were reported in France.[39] Thus, a minimal prevalence rate of ICA of approximately 1.38 per 1000 cases of invasive pneumococcal disease can be proposed. No comprehensive survey of the inherited risk factors underlying invasive pneumococcal disease had yet been undertaken, however. Therefore, beginning in January of 2005, we conducted a national prospective study on invasive pneumococcal disease to specifically address this question. To date, 110 patients have been enrolled, none of whom has been diagnosed with ICA. In a prospective study on invasive pneumococcal disease in children, Schutze et al[13] reviewed 2581 invasive pneumococcal infections recorded between 1993 and 1999 in the United States. Twenty-two of these patients had asplenia, and 3 of them had ICA. Median age at onset of infection was 12.5 months, significantly lower than in the 10 children who had undergone splenectomy.

The present study included 20 children and adults with ICA. An AD mode of inheritance was plausible in 4 of 10 families. The literature reported 24 sporadic and 26 familial cases of ICA, including 11 multiplex kindreds (7/11 with 2 cases and 4/11 with 3 cases). Among these, AD inheritance was suggested in 6 multiplex families, whereas AD or AR inheritance was possible in 5 families (including 2 consanguineous families). Information regarding consanguinity was not available for the single-case families. The rarity of consanguineous families compared with AR primary

immunodeficiencies in France, along with the overt AD pattern of inheritance in many families, strongly suggest that ICA is AD in most families. Sporadic cases may reflect either the low penetrance of ICA or de novo mutations. Determining whether the few families with an apparently "autosomal recessive" inheritance are truly AR, reflecting the genetic heterogeneity of ICA (allelic or nonallelic), or whether they reflect an AD inheritance with either parental mosaicism or incomplete penetrance in a genetically affected parent, is difficult.

The mode of revelation was severe invasive bacterial infection in 8 of the 10 index cases. *S pneumoniae* was the leading infectious agent. Rather unexpectedly, there were no documented infections by *H influenzae* type b or by *N meningitidis* in our series, despite the lack of vaccination for *Neisseira* in France. In other publications, of 45 reported cases of ICA presenting with severe or overwhelming sepsis (16 deaths), *S pneumoniae* was involved in 23 cases (51%; serotype 6B and 19F in 2 different patients), and *H influenzae* type b was involved in 4 cases (8.9%); there was no documented infection caused by *N meningitidis*. In the 4 kindreds (families A, C, D and E) with 7 symptomatic relatives, 4 died of infection, underscoring the importance of investigating all first- and second-degree relatives of patients with ICA.

Our study also indicates that ICA is symptomatic and life-threatening in childhood but tends to have a more favorable course, with a decreasing incidence of severe infections, with age. One hypothesis to explain the less-severe prognosis of ICA in adults would be the development of adaptive immune responses that bypass the spleen. Clinical immunologic data suggest that asplenia does not prevent effective T and B cell responses; however, T and B cell responses have not been studied in depth in these patients. Resident macrophages of the spleen play a major role in host defenses against septicemia. Splenic marginal zone B lymphocytes can produce neutralizing antibodies to a wide range of infectious agents; however, their role remains partially undefined.[40-42] Patients may have merely benefited from the better quality of medical care provided after diagnosis of ICA (ie, vaccinations, antibiotic prophylaxis, and prompt antibiotic treatment of febrile episodes). The relative clinical improvement of ICA with age is in keeping with the description of ICA in adults with thrombosis and very few (if any) infections.[17,30,31,43] ■

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References

1. Ivemark BI. Implications of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood: an analysis of the heart malformations in the splenic agenesis syndrome, with fourteen new cases. Acta Paediatr Suppl 1955;44(Suppl 104):7-110.
2. Rose V, Izukawa T, Moes CA. Syndromes of asplenia and polysplenia: a review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis. Br Heart J 1975;37:840-52.
3. Simpson J, Zellweger H. Familial occurrence of Ivemark syndrome with splenic hypoplasia and asplenia in sibs. J Med Genet 1973;10:303-4.
4. Alonso S, Pierpont ME, Radtke W, Martinez J, Chen SC, Grant JW, et al. Heterotaxia syndrome and autosomal dominant inheritance. Am J Med Genet 1995;56:12-5.
5. Casey B, Devoto M, Jones KL, Ballabio A. Mapping a gene for familial situs abnormalities to human chromosome Xq24-q27.1. Nat Genet 1993;5:403-7.
6. Belmont JW, Mohapatra B, Towbin JA, Ware SM. Molecular genetics of heterotaxy syndromes. Curr Opin Cardiol 2004;19:216-20.
7. Gebbia M, Ferrero GB, Pilia G, Bassi MT, Aylsworth A, Penman-Splitt M, et al. X-linked situs abnormalities result from mutations in ZIC3. Nat Genet 1997;17:305-8.
8. Zhu L, Belmont JW, Ware SM. Genetics of human heterotaxias. Eur J Hum Genet 2006;14:17-25.
9. Chen H. Atlas of Genetic Diagnosis and Counseling. Totowa, NJ: Humana Press; 2006.
10. Biggar WD, Ramirez RA, Rose V. Congenital asplenia: immunologic assessment and a clinical review of eight surviving patients. Pediatrics 1981;67:548-51.
11. Kaplan SL, Mason EO, Jr., Wald E, Tan TQ, Schutze GE, Bradley JS, et al. Six-year multicenter surveillance of invasive pneumococcal infections in children. Pediatr Infect Dis J 2002;21:141-7.
12. Murdoch IA, Anjos RD, Mitchell A. Fatal pneumococcal septicaemia associated with asplenia and isomerism of the right atrial appendages. Br Heart J 1991;65:102-3.
13. Schutze GE, Mason EO, Jr, Barson WJ, Kim KS, Wald ER, Givner LB, et al. Invasive pneumococcal infections in children with asplenia. Pediatr Infect Dis J 2002;21:278-82.
14. Waldman JD, Rosenthal A, Smith AL, Shurin S, Nadas AS. Sepsis and congenital asplenia. J Pediatr 1977;90:555-9.
15. Gonzalez M, Collaud S, Gervaz P, Morel P. Congenital asplenia (Ivemark syndrome) revealed by mesenteric vein thrombosis in a 77 year old patient. Gastroenterol Clin Biol 2007;31:860-2.
16. Myerson RM, Koelle WA. Congenital absence of the spleen in an adult: report of a case associated with recurrent Waterhouse-Friderichsen syndrome. N Engl J Med 1956;254:1131-2.
17. Chanet V, Tournilhac O, Dieu-Bellamy V, Boiret N, Spitz P, Baud O, et al. Isolated spleen agenesis: a rare cause of thrombocytosis mimicking essential thrombocythemia. Haematologica 2000;85:1211-3.
18. Dyke MP, Martin RP, Berry PJ. Septicaemia and adrenal haemorrhage in congenital asplenia. Arch Dis Child 1991;66:636-7.
19. Feder HM, Jr., Pearson HA. Assessment of splenic function in familial asplenia. N Engl J Med 1999;341:210-2.
20. Ferlicot S, Emile JF, Le Bris JL, Cheron G, Brousse N. Congenital asplenia: a childhood immune deficit often detected too late. Ann Pathol 1997;17:44-6.
21. Germing U, Perings C, Steiner S, Peters AJ, Heintzen MP, Aul C. Congenital asplenia detected in a 60-year-old patient with septicemia. Eur J Med Res 1999;4:283-5.
22. Gilbert B, Menetrey C, Belin V, Brosset P, de Lumley L, Fisher A. Familial isolated congenital asplenia: a rare, frequently hereditary dominant condition, often detected too late as a cause of overwhelming pneumococcal sepsis. Report of a new case and review of 31 others. Eur J Pediatr 2002;161:368-72.
23. Gill DG, Kara M. Septicaemia and adrenal haemorrhage in congenital asplenia. Arch Dis Child 1991;66:1366-7.
24. Gillis J, Harvey J, Isaacs D, Freelander M, Wyeth B. Familial asplenia. Arch Dis Child 1992;67:665-6.
25. Gopal V, Bisno AL. Fulminant pneumococcal infections in "normal" asplenic hosts. Arch Intern Med 1977;137:1526-30.
26. Honigman R, Lanzkowsky P. Isolated congenital asplenia: an occult case of overwhelming sepsis. Am J Dis Child 1979;133:552-3.

27. Kanthan R, Moyana T, Nyssen J. Asplenia as a cause of sudden unexpected death in childhood. Am J Forensic Med Pathol 1999;20:57-9.
28. Katcher AL. Familial asplenia, other malformations, and sudden death. Pediatrics 1980;65:633-5.
29. Kevy SV, Tefft M, Vawier GF, Rosen FS. Hereditary splenic hypoplasia. Pediatrics 1968;42:752-7.
30. Lindor NM, Smithson WA, Ahumada CA, Michels VV, Opitz JM. Asplenia in two father–son pairs. Am J Med Genet 1995;56:10-1.
31. Rose C, Quesnel B, Facon T, Fenaux P, Jouet JP, Bauters F. Congenital asplenia, a differential diagnosis of essential thrombocythemia (letter). Presse Med 1993;22:1748.
32. Tarlinton D, Light A, Metcalf D, Harvey RP, Robb L. Architectural defects in the spleens of Nkx2-3–deficient mice are intrinsic and associated with defects in both B cell maturation and T cell–dependent immune responses. J Immunol 2003;170:4002-10.
33. Thiruppathy K, Privitera A, Jain K, Gupta S. Congenital asplenia and group B streptococcus sepsis in the adult: case report and review of the literature. FEMS Immunol Med Microbiol 2008;53:437-9.
34. Gates AJ, Black S. Isolated congenital hyposplenia (ICH) in two generations of a non-consanguineous family [abstract]. Am J Hum Genet 1986; 39:A61.
35. Ahmed SA, Zengeya S, Kini U, Pollard AJ. Familial isolated congenital asplenia: case report and literature review. Eur J Pediatr 2009;169:315-8.
36. Araujo AR, Maciel I, Lima L, Chacim I, Barbot J. Congenital asplenia and severe visceral toxocariasis (letter). Pediatr Infect Dis J 2008;27:478.
37. Bertran SK, Donoso FA, Cruces RP, Diaz RF, Arriagada SD. Congenital asplenia and pneumococcal purpura fulminans in a pediatric patient: case report with pathological findings and review. Rev Chilena Infectol 2009;26:55-9.
38. Halbertsma FJ, Neeleman C, Weemaes CM, van Deuren M. The absent and vanishing spleen: congenital asplenia and hyposplenism—two case reports. Acta Paediatr 2005;94:369-71.
39. Varon E, Janoir C, Gutmann L. Centre national de référence des pneumocoques. Rapport d'activité 2008. Available from: http://www.invs.sante.fr/surveillance/index.html. Accessed September 14, 2009.
40. Weller S, Braun MC, Tan BK, Rosenwald A, Cordier C, Conley ME, et al. Human blood IgM "memory" B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire. Blood 2004;104:3647-54.
41. Weller S, Faili A, Garcia C, Braun MC, Le Deist FF, de Saint Basile GG, et al. CD40-CD40L independent Ig gene hypermutation suggests a second B cell diversification pathway in humans. Proc Natl Acad Sci USA 2001;98:1166-70.
42. Weller S, Mamani-Matsuda M, Picard C, Cordier C, Lecoeuche D, Gauthier F, et al. Somatic diversification in the absence of antigen-driven responses is the hallmark of the $IgM^+IgD^+CD27^+$ B cell repertoire in infants. J Exp Med 2008;205:1331-42.
43. Takahashi F, Uchida K, Nagaoka T, Honma N, Cui R, Yoshioka M, et al. Isolated congenital spleen agenesis: a rare cause of chronic thromboembolic pulmonary hypertension in an adult. Respirology 2008;13:913-5.

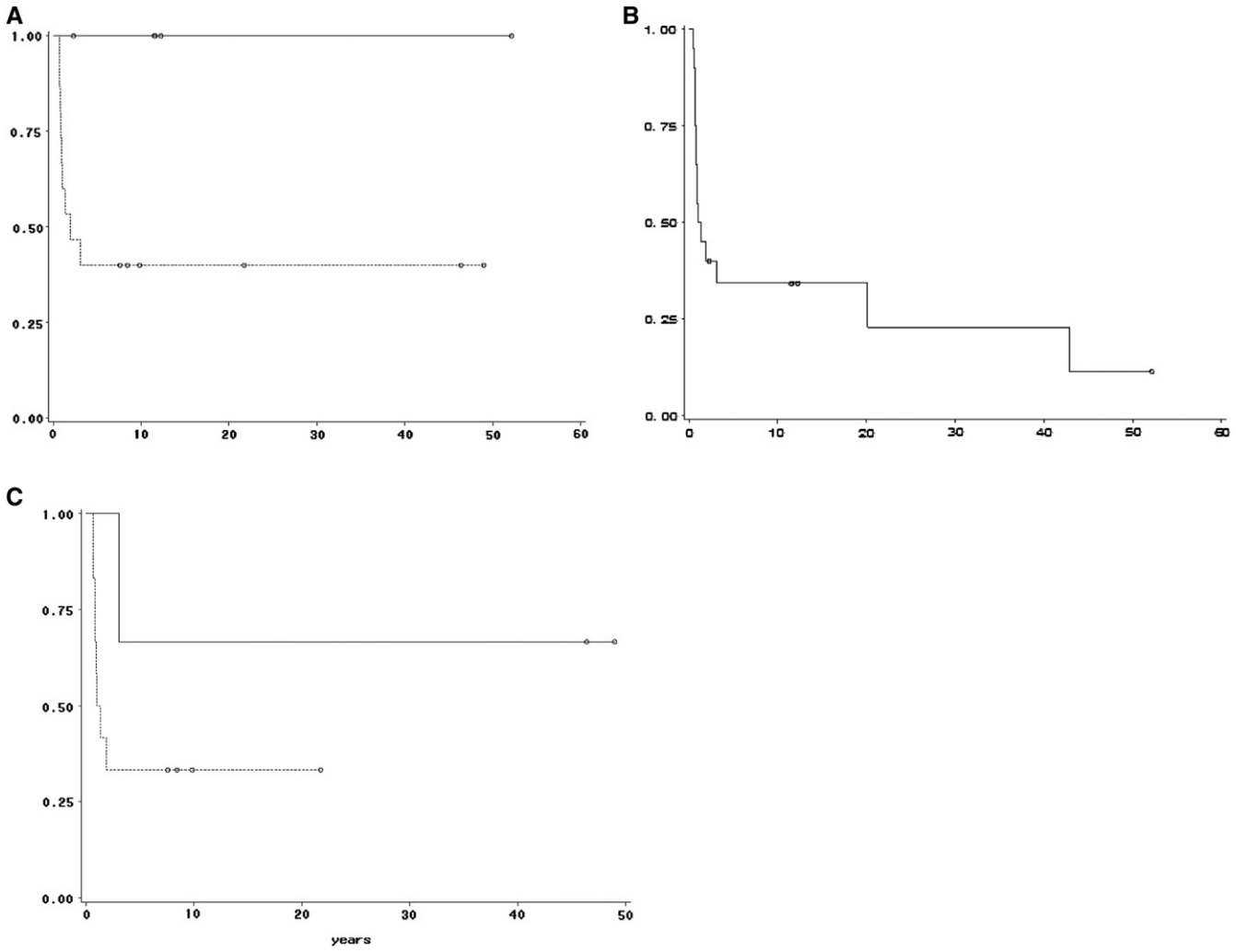

Figure 2. **A**, Overall survival of the 20 ICA patients according to infections (log rank = 0.041). **B**, Infection free survival of the 20 ICA patients. **C**, Survival analysis according to age at first infection (age $\leq$ 2 years, dotted line versus > 2 years, full line) (log rank = 0.232).