

Familial Hypogammaglobulinemia

Genetic Linkage With α_1 -Antitrypsin Deficiency

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• Familial hypogammaglobulinemia was found to exist in a large kindred. Phenotyping of α_1 -antitrypsin in 31 persons from seven families related to the patient in the index case suggests linkage of hypogammaglobulinemia with the protease inhibitor locus for α_1 -antitrypsin.

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Hypogammaglobulinemia comprises a heterogeneous group of disorders. Except for the genetically well-defined X-linked hypogammaglobulinemia, most cases of antibody deficiency are variable in clinical manifestation and different from each other in the mechanisms causing the defect, hence the term, "common variable hypogammaglobulinemia."^{1,2} In contrast to X-linked hypogammaglobulinemia, which manifests itself early in life, common variable hypogammaglobulinemia is late in onset and is usually termed "acquired"—although, in most cases, the mode of acquisition of the disease is unknown.

Few family studies have been performed on common variable hypogammaglobulinemia, but it seems that a subset of hypogammaglobulinemia exists that is probably familial, with an unclear mode of inheritance. Kirkpatrick and Schimke³ have reported familial hypogammaglobulinemia with low IgM as a marker, especially on the paternal side of the family. Another study has shown a quantitative deficiency in the expression of the Gm gene, which codes for the constant part of the IgG heavy chain in families with primary antibody deficiency⁴; however, this study failed to show a specific mode of inheritance.

α_1 -antitrypsin deficiency is a disease that has been well defined, both genetically and biochemically.^{5,6} The locus controlling the production of α_1 -antitrypsin is termed "protease inhibitor" (Pi) with polymorphic expression. The most common phenotype associated with α_1 -antitrypsin production is MM, whereas the phenotype ZZ is associated with α_1 -antitrypsin deficiency and clinical manifestations of neonatal hepatitis or emphysema. The heterozygous states MZ, MS, and SZ have a probable increased risk of emphysema, especially if associated with smoking.

The occurrence of both hypogammaglobulinemia and α_1 -antitrypsin deficiency in a large family permits us to define a subset of familial hypogammaglobulinemia, which is determined by a regulatory gene probably linked with the Pi locus.

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Serum Immunoglobulin Determinations and Protease Inhibitor Phenotyping in Families Related to Proband				
Relationship to Proband	Phenotype	IgG, mg/dL*§	IgA, mg/dL†§	IgM, mg/dL‡§
Family 1				
Proband	ZZ	262	18	27
Father	M ₂ Z	969	197	42
Mother	SZ	678	56	49
Family 2				
Paternal uncle	M ₂ Z	907	162	73
Spouse of paternal uncle (above)	MM	1321	238	159
Cousin	MM	969	184	68
Spouse of cousin (above)	MM	937	201	178
Second cousin	MM	603	108	38
Cousin	MZ	871	113	66
Family 3				
Paternal aunt
Cousin	MZ	1411	134	114
Second cousin	ZZ	1065	51	97
Family 4				
Paternal aunt	M ₂ S	693	83	146
Family 5				
Paternal aunt	M ₂ S	581	210	60
Spouse of paternal aunt (above)	MS	524	89	54
Cousin	MS	1111	305	55
Second cousin	MM	832	165	182
Second cousin	MM	967	118	186
Second cousin	MS	1061	199	87
Second cousin	MS	1034	184	89
Cousin	M ₂ S	589	208	85
Second cousin	M ₂ M	718	199	88
Second cousin	M ₂ S	1004	263	153
Family 6				
Maternal aunt	...	1058	148	368
Cousin	M ₁ Z	895	149	211
Family 7				
Maternal aunt	MS	704	102	149
Cousin	MS	613	110	248
Cousin	MM	1119	86	249
Spouse of cousin (above)	MM	621	92	288
Second cousin	MM	768	84	86
Second cousin	MM	620	104	76
Second cousin	MM	1073	83	201

*Normal range, 747 to 1,159 mg/dL.

†Normal range, 67 to 161 mg/dL.

‡Normal range, 85 to 183 mg/dL.

§Italicized numbers signal low Ig levels.

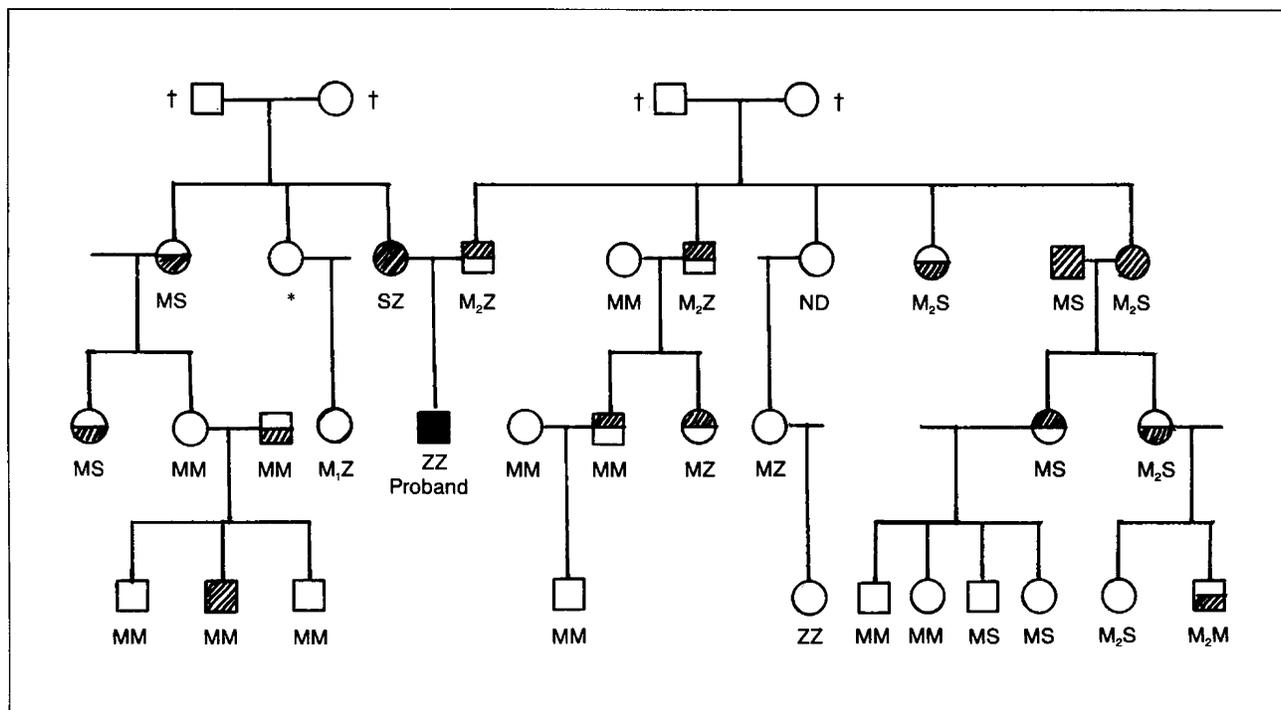
||Infants (IgG levels recorded are normal in infants).

SUBJECTS AND METHODS

Subjects

Thirty-one persons in seven families were studied for serum immunoglobulins and Pi phenotyping. Twenty-seven were relatives of the patient in the index case, a detailed study of whom has been reported elsewhere⁷ (the proband had no siblings or children). Four persons studied were spouses unrelated to the patient in the index case.

Emphysema and severe α_1 -antitrypsin deficiency with ZZ phe-



Pedigree showing familial hypogammaglobulinemia and abnormal α_1 -antitrypsin phenotypes. Boxes indicate male family members; circles, female family members; white boxes and circles, normal Ig; full black box, proband (with panhypogammaglobulinemia); upper-half black boxes and circles, low IgM; lower-half black boxes and circles, low IgG; ND, Ig determinations not performed; dagger, deceased; and asterisk, phenotyping not done.

notype were found in the index patient, in association with panhypogammaglobulinemia and hyperreactive airways disease. Immunologic studies of the mechanism of hypogammaglobulinemia disclosed no intrinsic B-cell defect, synthesis abnormality, or impairment of secretion of immunoglobulins. A serum suppressive factor was present and probably accounted for the hypogammaglobulinemia.⁷

Methods

Determination of serum IgG, IgA, and IgM levels was performed with nephelometry.⁸ Protease inhibitor phenotyping was performed on polyacrylamide gel electrophoresis with isoelectric focusing.⁹

RESULTS

The results of serum immunoglobulin determinations and Pi phenotyping are listed in the Table. Family pedigree is illustrated in the Figure. Fourteen persons from three generations were found to have low immunoglobulin levels, with panhypogammaglobulinemia, low IgM, low IgG, or both (low IgM and IgG levels, but not low IgA). Of these 14, 11 were heterozygous for the Pi locus, while only two had normal phenotype MM. The proband was homozygous with phenotype ZZ and panhypogammaglobulinemia. Two spouses of individuals related to the proband were also found to have low immunoglobulin levels, one with MS phenotype and low IgM and IgG, the other with MM phenotype and low IgG.

COMMENT

Familial hypogammaglobulinemia has been shown to exist in this study of a large kindred. Affected individuals were found in all three generations, thus pointing to a

dominant mode of inheritance. Furthermore, phenotyping of α_1 -antitrypsin suggests that the locus determining hypogammaglobulinemia is probably linked to the Pi locus. Cross-over mechanisms probably accounted for the exceptions in two individuals with low immunoglobulin levels and normal phenotype MM.

Although no other immunologic studies regarding the mechanism of the hypogammaglobulinemia were performed, except in the index case, it did not appear that the defect was structural. This was due to the variable degree of hypogammaglobulinemia in affected individuals. Our previous study,⁷ investigating the mechanism of hypogammaglobulinemia in the same proband, demonstrated a serum-suppressive factor capable of preventing the pokeweed mitogen-induced differentiation of B lymphocytes in both the patient and normal donor. This supported the hypothesis that a regulatory nature exists for the genetic defect that is responsible for the hypogammaglobulinemia observed in this large kindred.

The clinical importance of the combination of hypogammaglobulinemia and α_1 -antitrypsin deficiency, either homozygous or heterozygous, is unclear. However, it is expected that frequent pulmonary infections, secondary to hypogammaglobulinemia, would accelerate the lung parenchymal destruction in α_1 -antitrypsin-deficient patients, because of dysequilibrium occurring between elastase released from neutrophils recruited to fight infection and the deficient protease inhibitor system.

More Pi phenotyping in patients with hypogammaglobulinemia and their relatives is necessary to study further the linkage and the clinical effects of this combination of genetic defects.

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Tracheobronchial Papillomatosis With Malignant Transformation

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• A 31-year-old man had tracheobronchial papillomatosis that rapidly evolved into squamous cell carcinomatosis. This unusual event has rarely been recorded previously. Herein the natural history of the disease is analyzed on the basis of the existing literature on papillomatosis. (*Arch Intern Med* 1983;143:577-578)

Papilloma of the tracheobronchial tree is a rare tumor in adults, whereas papilloma of the larynx is the most common respiratory tract tumor in infants and children. The lesion usually remains confined to the larynx, and it rarely extends into the trachea and, even more rarely, into the bronchi. The following describes an adult patient, without any known predisposing factors, who had multiple papillomas of the tracheobronchial tree that underwent rapid malignant transformation.

REPORT OF A CASE

A 31-year-old man had a two-week history of cough associated with yellow and blood-streaked expectoration. He had a low-grade fever and experience increasing dyspnea on exertion. He had smoked one pack of cigarettes a day for the past five years, and he admitted to a heavy alcohol consumption. He worked as a carpenter and had no unusual hobbies or exposure to animals. On

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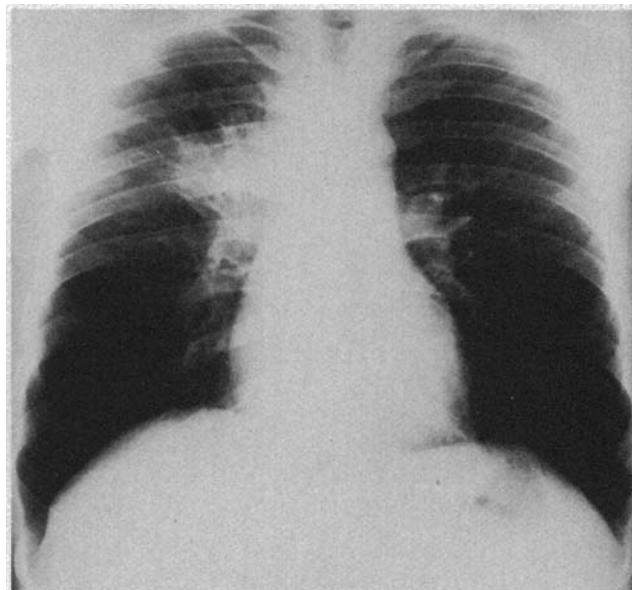
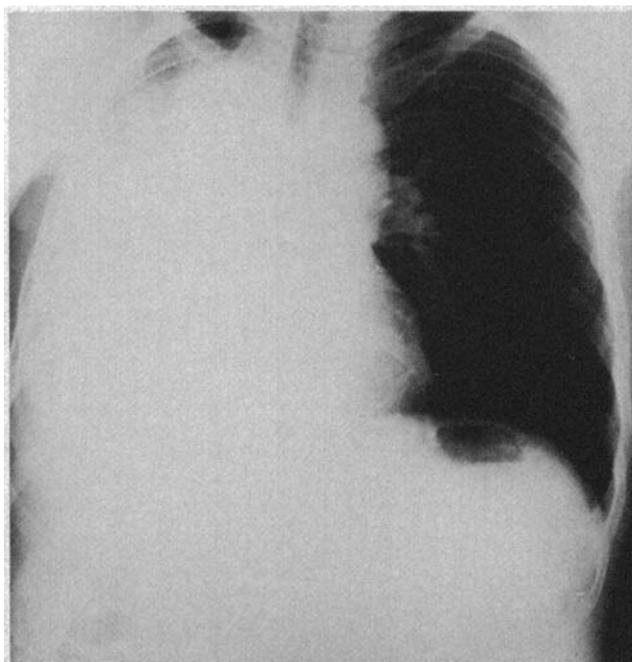


Fig 1.—Chest roentgenogram on first hospital day (June 23, 1981) showing right paratracheal mass, with postobstructive consolidation and loss of volume.

Fig 2.—Chest roentgenogram on 26th hospital day (July 18, 1981) showing atelectasis of right lung.



admission to the hospital, he had a temperature of 38.5 °C; findings from the remainder of his physical examination were normal, except for early clubbing. Chest roentgenogram showed a right paratracheal mass with an infiltrate and loss of volume in the upper part of the right lobe (Fig 1). His sputum showed mixed flora on Gram's stain, but it was negative for acid-fast bacteria on several smears. He was anergic to 5 tuberculin units of PPD, mumps, *Candida*, and coccidioidomycosis antigens.

He was given oral erythromycin stearate therapy, but the patient continued to have cough and fever, and antituberculosis