Selective γ -A-globulin Deficiency, with Dominant Autosomal Inheritance in a Swiss Family

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The synthesis of immunoglobulins seems to be genetically determined, but to our knowledge there have not been any descriptions of selective γ -A-globulin deficiency with a clear mode of inheritance. This report describes a Swiss family in which a selective γ -A-globulin deficiency of probable dominant autosomal inheritance could be demonstrated in members of two generations. The biological significance of the γ -A-globulin fraction in man is still obscure, but in those of this family affected with the defect a history of recurrent infections was present in some but absent in others.

Material and Methods

The three immunoglobulins were determined in serum and saliva by means of a single radial diffusion method (Immuno-Plates, Hyland Lab., Calif.) (Mancini *et al.*, 1964; Stege, 1968). The results in serum were indicated first in a percentage of normal adult values. As standard we took a pool of 200 sera of healthy adult blood donors. For conversion into absolute values in mg./100 ml., we calculated from the following normal values: 1000 mg./100 ml. γ -G, 200 mg./100 ml. γ -A, and 90 mg./100 ml. γ -M (Gitlin, 1966; Stiehm and Fudenberg, 1966). The lowest figure detectable by this method is 5 mg./100 ml. γ -globulin.

A quantitative relation between the immunoglobulins is given; it was not possible to determine quantitatively γ -globulins in saliva, and normally there is more γ -A than γ -G-globulin (Stoelinga and van Muuster, 1965).

All serum samples were also examined by means of paper and immunoelectrophoresis.

Results

The proband, a 7-year-old girl, was admitted for evaluation of hypertension. As she suffered from recurrent infections of the upper respiratory tract, a possible antibody deficiency was looked for. Examination revealed a complete selective γ -A-globulin deficiency, and the child's mother, who in her youth had suffered from such recurrent

infections, also showed the same complete defect. Consequently we examined three generations of the family. The pedigree is shown (Fig.). In order to simplify the review of the case history of the individual members of the family we present the important data in the Table.

Discussion

There is good evidence of a selective γ -A-globulin deficiency in 5 members of the family reported; in 4 no γ -A-globulin could be found. All those examined showed, beside the above-mentioned γ -A-globulin deficiency, no other lack of an immunoglobulin. Therefore, we cannot compare this family with the cases of Wollheim *et al.* (1964), who found a selective incomplete deficiency of γ -A-globulin in relatives of patients with a general hypo- γ -globulinaemia.

It is probable that the γ -A-globulin deficiency in this family is due to a defect of synthesis. We found no signs of an enteral or renal loss of proteins, nor of an invasion of the bone-marrow by pathological cells. An accelerated breakdown of the γ -A-globulins by antibodies is not yet excluded, but this hypothesis is unlikely.

Genetic aspect. All forms of selective γ -A-globulin deficiency known until now are summarized as follows.

(1) *Accompanying another disease.* (a) In most of the cases of ataxia telangiectasia, a disease inherited in an autosomal recessive way (Ammann *et al.*, 1965; Peterson, Kelly, and Good, 1964; Fireman, Boesman, and Gitlin, 1964); (b) in some cases of steatorrhoea, probably representing a primary defect (Heremans, Crabbé, and Masson, 1966).

(2) *Other forms.* (a) In adults with normal families (Stoelinga and van Muuster, 1965; Rockey *et al.*, 1964); (b) in adults with relations who have a hypo- or a γ -globulinaemia (Wollheim *et al.*, 1964; Wollheim and Williams, 1965; Rockey *et al.*, 1964);

FIG.—Pedigree of a Swiss family showing a selective γ -A-globulin deficiency in two generations. $\circ$ died.

TABLE
Summary of Findings in Family Members

Pedigree No.*	Sex	Year of Birth	History of Recurrent Infection†	Immunoglobulins in Serum (diffusion method) (mg./100 ml.)			Immunoglobulins in Saliva‡ (diffusion method)			Comments
				IgA	IgG	IgM	IgA	IgG	IgM	
IV. 1	F	1959	+	Nil	1080	71	Nil	Nil	Nil	Propositus
IV. 2	M	1961	Nil	9	1120	48	Nil	Nil	Nil	
IV. 3	M	1964	+	50	810	110	—	—	—	
IV. 4	F	1966	Nil	—	—	—	—	—	—	Not examined
IV. 5	M	1965	Nil	Nil	940	66	—	—	—	
III. 1	M	1929	Nil	128	960	66	++	+	Nil	
III. 2	F	1934	(+)	Nil	1100	68	Nil	(+)	+++	Died at 1 yr. from pneumonia
III. 3	F	1939	+	—	—	—	—	—	—	
III. 4	F	1941	Nil	Nil	1100	102	Nil	++	+	Refused examination, healthy
III. 5	M	1937	Nil	—	—	—	—	—	—	Died at 10 yr. from hypernephroma (immunoelectrophoresis normal)
III. 6	F	1945	Nil	—	—	—	—	—	—	
II. 1	F	—	—	—	—	—	—	—	—	Died at 20 yr. from tuberculosis
II. 2	M	—	—	—	—	—	—	—	—	Died in newborn period, cause unknown
II. 3	M	1909	Nil	180	1100	120	—	—	—	Dwarfism, debility
II. 4	F	—	—	—	—	—	—	—	—	Died at 7 yr. from unknown cause
II. 5	F	1913	Nil	135	1060	100	—	—	—	
II. 6	F	—	—	—	—	—	—	—	—	Died at few weeks from unknown cause
II. 7	M	1898	Nil	—	—	—	—	—	—	Silicosis, coxarthrosis (immunoelectrophoresis shows intensified lines of γ -A- and γ -G-globulins)
II. 8	F	—	Nil	—	—	—	—	—	—	Refused examination, coxarthrosis
II. 9	F	—	Nil	—	—	—	—	—	—	Not examined, healthy
II. 10	M	—	—	—	—	—	—	—	—	Died, no statements available
II. 11	M	—	Nil	—	—	—	—	—	—	Refused examination, healthy
II. 12	M	1909	Nil	198	1040	82	—	—	—	
II. 13	F	1909	Nil	200	1100	75	++	+	(+)	
II. 14	F	—	Nil	—	—	—	—	—	—	Not examined, healthy
I. 1	M	—	—	—	—	—	—	—	—	Died at 62 yr. from tuberculosis
I. 2	F	—	—	—	—	—	—	—	—	Died from unknown cause
I. 3	M	—	—	—	—	—	—	—	—	Died at 82 yr. from carcinoma
I. 4	F	—	—	—	—	—	—	—	—	Died at 82 yr.

*The figures correspond to those in Fig. 1

†+ = Recurrent infections of upper respiratory tract; (+) = Recurrent infections during childhood; — History not available.

‡— = Not examined; Nil = examined but not detectable; (+) = trace.

(c) in infants, as a transitory deficiency because of a retarded maturation of the globulin synthesis.

Despite exhaustive searches of the literature, no previous reports of a familial selective γ -A-globulin deficiency without any other disease, have been found, either by us or by other authors.

Stoelinga and van Muuster (1965) examined the family of a 6-year-old boy with a selective γ -A-globulin deficiency: all relatives had normal immunoglobulins. Rockey *et al.* (1964) looked in vain for a γ -A-globulin lack in the families of two unrelated men with selective γ -A-globulin deficiency. They assumed a defect of the synthesis of the heavy chains of the γ -A-globulins. There are two separate reports of Wollheim *et al.* (1964) and Wollheim and Williams (1965); one examined the families of 9 patients with an 'acquired' hypo- γ -globulinaemia and found members with different immunoglobulin deficiencies, e.g. persons with a low level of γ -A-globulin. The second paper described 6 families of patients with 'acquired' hypo- γ -globulinaemia, in which 3 families were normal, and 3 others (consanguineous families) had different immunoglobulin deficiencies; only one person showed a selective γ -A-globulin deficiency. In their discussion the authors doubt whether the complete absence of γ -A-globulin can be explained on a genetic base. Selective γ -A-globulin deficiency accompanying another disease gives a different picture: in most of the cases of ataxia telangiectasia, a complete or partial deficiency of this immunoglobulin is found, sometimes combined with a lymphopenia and thymic hypoplasia. The neurological disease has an autosomal recessive mode of inheritance.

In our family of 5 cases with the defect in two generations, there is probably a defect of synthesis with an autosomal dominant inheritance showing a variable degree of penetration.

Clinical aspect. Many authors are interested in the biological role of the γ -A-globulin. We have found reports on γ -A-globulin deficiency without any clinical sign (Wollheim *et al.*, 1964; Wollheim and Williams, 1965; Rockey *et al.*, 1964), as well as reports of recurrent infections of the upper respiratory tract (West, Hong, and Holland, 1962; Stoelinga and van Muuster 1965). This could probably be explained by the fact that the γ -A-globulins are the most important fraction of immunoglobulins in exocrine fluids such as saliva and bronchial secretion (Remington *et al.*, 1964; Gitlin, 1966; Rossen *et al.*, 1966) in the form of 11 S globulins. West *et al.* (1962) looked at 13 children with a selective γ -A-globulin deficiency:

in 4 they found recurrent infections of the upper respiratory tract, and in 4 children there was brain damage and less often other signs. The authors came to the conclusion that no constant clinical sign is specific for a γ -A-globulin deficiency. Stoelinga and van Muuster (1965) gave a review of the antibodies in the γ -A-fraction. It is interesting that all the antibodies mentioned are not specific for the γ -A-fraction, but may also be found in the other globulin fractions. More recent examinations show that not even the reagins which, until recently, have been thought to be γ -A-globulin specific, are found in this fraction (Ishizaka and Ishizaka, 1966). It is obvious that the human organism may adapt completely to a deficiency of γ -A-globulin, even in the exocrine fluids. Rockey *et al.* (1964) and Tomasi *et al.* (1965) found no γ -A-globulin in the saliva of their patients with γ -A-globulin deficiency, but they did find γ -G-globulin and γ -M-globulin.

Of those with γ -A-globulin deficiency in our family, one child and one woman suffered recurrent infection of the upper respiratory tract and 3 others were clinically normal. Moreover, at least one child with normal immunoglobulins suffered recurrent infections. Thus, we doubt whether infection is related to γ -A-globulin deficiency. Despite a search for compensatory mechanisms, we found no significant differences in the blood smears or in the blood level of γ -G and γ -M globulin, but there was a possible compensatory increase of salivary γ -G and γ -M-globulins in 2 cases.

Summary

A Swiss family is described in which 4 members from 2 generations showed a selective complete γ -A-globulin deficiency. It is suggested that the mode of inheritance is probably an autosomal dominant gene.

This is thought to be the first report of a selective γ -A-globulin deficiency with a clear-cut hereditary pattern, and it supports the hypothesis of an independent genetic basis for the synthesis of specific heavy chains for γ -A-globulin.

A tendency to recurrent infection, though present in some, was not present in all those affected. Some problems arising from this difference are discussed, particularly the possibility of a compensatory increase in other immunoglobulins in exocrine fluids, such as the saliva.

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