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Evidence for this immunoglobulin A abnormality was also found in the proposita's mother and elder son, demonstrating it to be a hereditary disorder.

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A Hereditary Immunoglobulin A Abnormality:

Absence of Light-Heavy—Chain Assembly

STUDY OF IMMUNOGLOBULIN SYNTHESIS IN TONSILLAR CELLS

CHAYA MOROZ, JACOB AMIR, and ANDRE DE VRIES

From the Rogoff-Wellcome Medical Research Institute and the Department of Medicine D, Tel-Aviv University Medical School, Beilinson Hospital, Petah Tikva, Israel

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Evidence for this immunoglobulin A abnormality was also found in the proposita's mother and elder son, demonstrating it to be a hereditary disorder.

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INTRODUCTION

In recent years immunoglobulin A abnormalities have been described in various pathological conditions, such as IgA myeloma (1), α-chain disease, a special form of malignant lymphoma (2), a variety of "nonmalignant" diseases with deficiency of serum and secretory IgA (3–7), and as an isolated deficiency, familial hypo-

gammaglobulinemia-A (8, 9). Deficiency of IgA, normally preponderant in mucous secretions (10), has been held responsible for recurrent upper respiratory tract infections and/or gastrointestinal disturbances.

In the present communication we describe a new hereditary immunoglobulin A abnormality, not associated with malignancy, and characterized by the presence of free α-chains in the serum and saliva, and of free α-chains and free light-chains in the urine. Studies with tonsillar cells obtained from the proposita indicated the absence of α-chain to light-chain assembly. The immunoglobulin A abnormality in this family differs from that in α-chain disease in which no intracellular synthesis of light-chain was detected (2).

METHODS

Case report. The proposita, a 30 yr old Israel-born schoolteacher, was investigated for recurrent upper respiratory tract infections and tonsillitis, from which she had suffered since early childhood. The infections were so frequent as to interfere with her studies at school and later with her work as a teacher. She never had pneumonia and there was no history of recurrent gastrointestinal disturbances, nor of bulky stools. Her parents, her only brother, and her husband were healthy. Her elder son, 4½ yr of age, had a history of frequent upper respiratory tract infection, tonsillitis, otitis media, and twice severe gastroenteritis for which he had to be hospitalized. The patient's second son, 3 yr of age, seemed not to be prone to infections. Physical examination of the proposita was normal, except for enlarged tonsils. X-ray studies of the stomach and small intestines were normal. Fecal fat excretion was 5 gm per 24 hr. Routine blood and urine examinations including liver function tests were normal. The serum albumin was 4.2 g/100 ml, globulin 3.1 g/100 ml with a normal paper electrophoretic pattern. Serum immunoglobulin concentrations determined by radial immunodiffusion (11), using commercially available plates and stan-

dards were as follows: IgG 960 mg/100 ml, IgA 180 mg/100 ml, IgM 100 mg/100 ml (mean normal values 1200 ±300 mg/100 ml, 280 ±100 mg/100 ml, 88 ±22 mg/100 ml, respectively). The phagocytic and bactericidal capacities of the patient's neutrophils, determined by the method given by Douglas, Davis, and Fudenberg (12), as modified from the methods of Hirsch and Strauss (13), and Quie, White, Holmes, and Good (14), were found to be normal. The response of patient's peripheral blood lymphocytes to Phyto-hemagglutinin M[1] in vitro, as gauged by the extent of blastogenic transformation (15), was normal. To test delayed hypersensitivity, 0.1 ml of mumps antigen (Eli Lilly & Co.) was injected intradermally. The response was found to be normal with induration and erythema of 9 mm. Tonsillectomy was performed on 25 November 1969 by Dr. Levy of the Ear, Nose, and Throat department, and the tonsils were immediately placed in Spinner tissue culture medium. Physical examination of the above mentioned relatives was normal. Serum immunoglobulin concentrations could be examined thus far only in the proposita's father and elder son, and were in the former IgG 1100 mg/100 ml, IgA 190 mg/100 ml, IgM 80 mg/100 ml, and in the latter IgG 1000 mg/100 ml, IgA 140 mg/100 ml, IgM 60 mg/100 ml.

Immunological and chemical studies. Goat anti-human IgA serum monospecific for α-chain, anti-human IgM serum monospecific for μ-chain, anti-light-chain type K serum, and anti-light-chain type L serum were obtained from Miles-Yeda, Rehovoth. Rabbit anti-human IgA serum monospecific for α-chain, anti-human light-chain type K serum and two anti-human light-chain type L sera were obtained from Dr. E. C. Franklin (N. Y. U. School of Medicine) (16). Goat serum against Fc fragment of human IgG, horse antiserum and rabbit anti-goat γ G serum were obtained from Hyland.[2] Goat anti-human light-chain serum, precipitating both K and L light-chains, was kindly provided by Dr. J. B. Robbins (Albert Einstein School of Medicine). Anti-secretory piece (SP)[3] serum was prepared in rabbits as follows: 10 mg/ml of human colostrum were mixed v/v with complete Freund's adjuvant.[1] The emulsion was injected into the four foot pads (0.05 ml in each) and into the back skin (0.3 ml). Booster injections (0.5 ml) were given intramuscularly once a week for a period of 4 wk. 10 days after the last booster injection the animals were bled by cardiac puncture and antisera collected. The anti-colostrum serum was observed with normal human serum, following which it reacted with SP only.

Immunoelectrophoresis was performed with 1% agar gel in 0.05 M barbital buffer, pH 8.2. Ouchterlony agar diffusion studies were carried out in 1% agar in 0.15 M NaCl, pH 7.2.

Urinary concentration of type K and L light-chains, and the K:L light-chain ratio in isolated serum IgG were determined by radial immunodiffusion (11).

Reduction of isolated immunoglobulins (0.5–0.7%) was performed with 0.2 M 2-mercaptoethanol in 0.5 M Tris-HCl buffer, pH 8.0, under N_2 for 1 hr at room temperature. This was followed by alkylation with a 10% equivalent excess of iodoacetamide at pH 8.0 for 1 hr at room temperature. The reduced and alkylated material was dialyzed against 2000 vol of 0.01 M Tris-HCl buffer, pH 8.0, for 24 hr.

The reduced and nonreduced isolated immunoglobulins were run on disc electrophoresis in polyacrylamide at pH 8.6 according to the method of Davis (17), and at pH 7.1 in 0.1%

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[1] Difco Laboratories, Detroit, Mich.

[2] Hyland Laboratories, Inc., Los Angeles, Calif.

[3] *Abbreviations used in this paper:* 2-ME, 2-mercaptoethanol; SDS, sodium dodecyl sulfate; SP, secretory piece.

sodium dodecyl sulfate (SDS) according to the method of Shapiro, Viñuela, and Maizel (18). Markers for heavy- and light-chains, derived from the serum and urine of a IgA myeloma patient and from Bence Jones protein, containing urine of another myeloma patient, were kindly given to us by Dr. A. Pick.

Isolation of immunoglobulins

Salivary IgA. Saliva, collected after stimulation with chewing gum, was dialyzed against distilled water for 48 hr. The material was centrifuged at 10,000 rpm for 20 min, and the supernatant collected. The dialyzed saliva was concentrated 15- to 20-fold by lyophilization. The concentrated saliva was dialyzed against 0.01 M phosphate buffer, pH 7.4, before application to a column of DEAE-cellulose as described by Tomasi, Tan, Solomon, and Pendergast (10). A stepwise gradient of phosphate buffer: 0.01 M, pH 6.2 and 0.3 M, pH 4.8, was used. The material eluted with 0.1 M, pH 6.2 buffer was pooled, dialyzed overnight against 0.005 M phosphate buffer, pH 7.0, and lyophilized.

Serum immunoglobulins. The serum immunoglobulins were precipitated with ammonium sulfate solution at 40% saturation. IgG and IgA were isolated by DEAE-cellulose chromatography and Sephadex G-200 gel filtration as described by Newcomb, Normansell, and Stanworth (19). Pure IgG was eluted from the DEAE-cellulose with 0.005 M sodium phosphate buffer, pH 8.0. IgA, eluted from the DEAE-cellulose column, applying a linear gradient of phosphate buffer, pH 8.0 between 0.005 and 0.10 M, then chromatographed on Sephadex G-200, still contained traces of IgG. The contaminating IgG was absorbed with anti-human IgG bound to Sepharose according to the method described by Givol, Weinstein, Gorecki, and Wilcheck (20). The separation of IgM was carried out by gel filtration on Sephadex G-200, eluted with 0.1 M Tris-HCl (pH 8.0) in 0.2 M NaCl (21). The IgM containing fraction was twice rechromatographed.

Urinary immunoglobulins. Urine was dialyzed against distilled water for 48 hr, centrifuged at 10,000 rpm for 20 min, and concentrated 200-fold by lyophilization. The concentrated urine was applied to a Sephadex G-200 column (160 × 2.3 cm) and eluted with 0.15 M NaCl. A fraction which reacted with anti-α-, anti-γ-, and anti-light-chain sera was pooled, dialyzed, concentrated by lyophilization, and applied to a Sephadex G-100 column (90 × 2.3 cm). The proteins were eluted from the column with 0.15 M NaCl.

In vitro protein synthesis. Cells were teased from the proposita's tonsils and filtered through a stainless steel screen, washed three times, and resuspended in Eagle's medium (22) containing 1/100 the amount of amino acids (23). 10 ml of tonsillar cell suspension (1.3 × 10⁷ cells per ml) were pre-incubated for 20 min at 37°C, and then exposed to 30 μCi of amino acids-¹⁴C (Amersham-Searle Corp., Des Plaines, Ill.) for 3 hr at 37°C. Incorporation of the radioactive precursor was stopped by chilling to 4°C. The medium, containing the proteins secreted by the cells, was collected after centrifugation of the cell suspension at 1,000 rpm for 6 min. The cells were washed three times with cold medium and suspended in 2.5 ml of phosphate-buffered saline, pH 7.2, and lysed by freezing and thawing five times. The cell debris were removed after centrifugation and the cytoplasm collected. The amount of labeled amino acids incorporated into intracellular and extracellular protein was determined by precipitation with 5% trichloroacetic acid (TCA) at 4°C.

Immunoglobulin synthesis by tonsillar cells was determined by specific precipitation with anti-IgA, anti-IgG, anti-IgM,
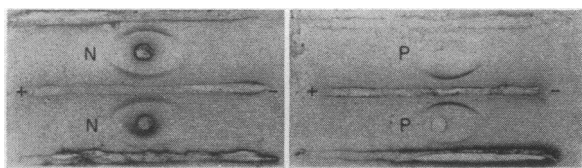
FIGURE 1 Immunoelectrophoresis of isolated patient's (P) and normal (N) salivary IgA using rabbit antisera, in troughs from top to bottom: anti-light-chain type L, anti-α chain, anti-SP. The normal and patient's IgA concentrations used were 0.8% and 1%, respectively.

FIGURE 2 Immunoelectrophoresis of isolated serum IgA using rabbit antisera, in troughs from top to bottom: anti-light-chain type L, anti-α-chain. Both patient's and normal IgA concentrations were 1%.

and anti-light-chain sera. 0.2 ml of the cell cytoplasm was mixed with 5 µl of goat anti-immunoglobulin sera for 1 hr at 37°C. The mixture was then reacted with 50 µl of rabbit anti-goat IgG for 1 hr at 37°C, and 4 hr at 4°C. The precipitate formed was collected after centrifugation at 10,000 rpm for 15 min, washed once with phosphate-buffered saline, pH 7.2, and suspended in 0.25 ml of 0.05 M phosphate buffer, pH 7.1. The precipitated immunoglobulin was characterized by acrylamide gel electrophoresis according to the method of Maizel (24). The sample was prepared for electrophoresis by treatment with 10% acetic acid, 1% SDS, 0.5 M urea and 1% 2-mercaptoethanol (2-ME) (25). The sample was dialyzed at room temperature for 16 hr against 0.01 M phosphate buffer, pH 7.1, containing 0.1% SDS, 0.5 M urea, 0.1% 2-ME, before gel electrophoresis.

Identification of the nascent proteins secreted into the medium was carried out by acrylamide gel electrophoresis in 0.01 M phosphate buffer, pH 7.1, 0.1% SDS, and 0.5 M urea, without reduction with 2-ME.

All the above procedures were performed also with the tonsils obtained from two control patients, subjected to tonsillectomy for recurrent tonsillitis, but having normal serum immunoglobulins.

RESULTS

Characterization of proposita's isolated immunoglobulins

Salivary immunoglobulins. Ouchterlony agar diffusion of the patient's concentrated saliva, using the antisera specific for the different immunoglobulin classes, revealed the presence of IgA and SP, traces of IgG, absence of IgM, and no precipitation arc with anti-light-chain sera types K and L. Immunoelectrophoresis of patient's isolated IgA (Fig. 1) showed it to form precipitin arcs with anti-α-chain serum and with anti-SP serum. Patient's IgA did not react with three anti-light-chain type L sera and with two anti-type K sera. IgA isolated from the control saliva reacted both with anti-L
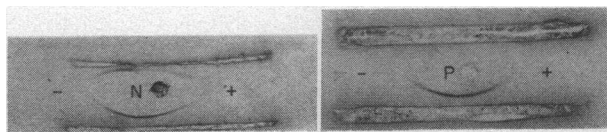
and anti-K serum (reaction with one rabbit anti-L serum shown in Fig. 1). Patient's reduced and alkylated IgA did not react with any of the anti-light-chain sera. The electrophoretic mobility on agar of patient's isolated IgA was different from that of salivary IgA from the normal control. Furthermore, patient's SP migrated to the same location as her IgA (Fig. 1), indicating it to be bound to the α-chain. On acrylamide gel electrophoresis patient's isolated salivary IgA migrated faster than normal IgA (Fig. 7). The difference in migration was verified by comparison with five different control samples.

Serum immunoglobulins. Immunoelectrophoresis of IgA isolated from the patient's serum showed it to react with anti-α-chain serum but not with anti-light-chain type L serum (Fig. 2), nor with type K sera. (Three anti-light-chain type L and two anti-light-chain type K sera were used.) The electrophoretic mobility on agar of patient's serum IgA was similar to that of normal serum IgA. Patient's isolated serum IgG (Fig. 3) and IgM reacted in immunoelectrophoresis with anti-γ- and anti-u-chain sera respectively and with anti-light-chain sera, types L and K. The ratio of L to K determinants in patient's serum IgG was 1:3, as compared with a ratio of 1:4 in the normal control serum IgG.

As shown in Fig. 4, serum IgA, run on acrylamide gel in SDS revealed a single major band corresponding to the heavy-chain monomer from an IgA myeloma. In addition there was a large amount of material which did not penetrate the gel and a series of faint bands migrating more slowly than the major one. After reduction and alkylation no light-chain band was released while the series of bands which migrated with an intermediate mobility increased in intensity, and the material at the origin largely disappeared. Although the precise nature of the intermediate band remains unknown, it seems possible that they represent heavy-chain polymers.
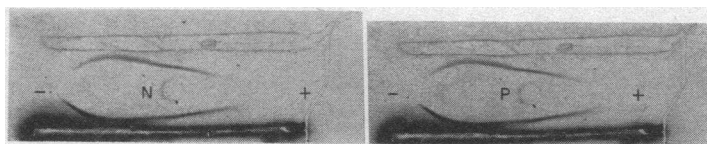

FIGURE 3 Immunoelectrophoresis of isolated serum IgG using in troughs from top to bottom: rabbit anti-light-chain type L, goat anti-Fc fragment. Both patient's and normal IgG concentrations were 1%.

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Urinary immunoglobulins. The total urinary soluble protein excreted by the patient in 24 hr amounted to 300 mg. As determined by radial immunodiffusion, the amount of light-chains was 214 mg and the ratio of the L to K determinants was 1:2.

Gel filtration chromatography of patient's concentrated urine on Sephadex G-200 yielded six fractions (Fig. 5). Fraction I reacted in Ouchterlony gel diffusion with anti-α-chain serum only; fractions II and III reacted with anti-light-chain serum only; fraction IV exhibited precipitin arcs with anti-light-chain serum, anti-γ-chain serum, and with anti-α-chain serum. The free light-chains in fractions II, III, and IV reacted with anti-light-chain sera type K and type L. Fraction VI was devoid of immunoglobulins as revealed by agar-gel diffusion; fraction V contained minute amounts of material reacting with anti-α-chain serum, anti-γ-chain serum, and anti-light-chain type K serum.

Since the α-chains (fraction I) were excluded from the Sephadex G-200 with a void volume, they were in polymerized form. When running both reduced and non-reduced fraction I after treatment with SDS on acrylamide gel (Fig. 6), their migration was identical.

Family study. Available for study were the proposita's mother and father, her only brother, her hus-
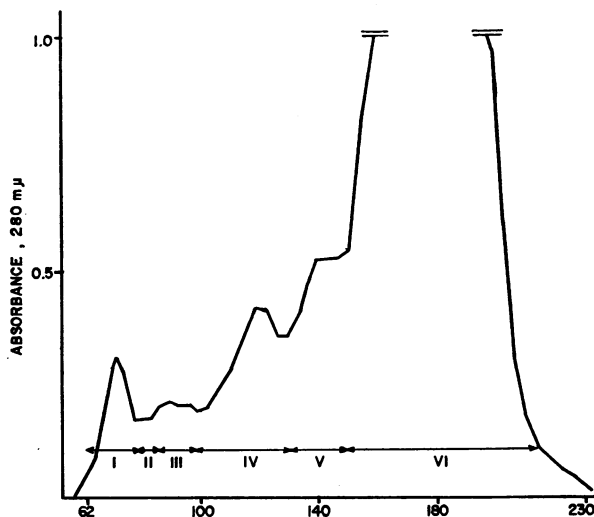

FIGURE 5 Chromatography of patient's concentrated urine on Sephadex G-200. Elution performed with 0.15 M NaCl, at flow rate 3 ml/10 min.

band, and her two sons. Examination of their saliva revealed the presence of free α-chains bound to SP and lack of free light-chains in the proposita's mother and elder son, while in the others normally assembled IgA was found. The electrophoretic mobilities in acrylamide gel of the IgA isolated from the saliva of the various family members are compared in Fig. 7. The salivary IgA from the proposita, her mother, and elder son migrated faster than normal. It is noteworthy that while the proposita's saliva contained only traces of IgG,
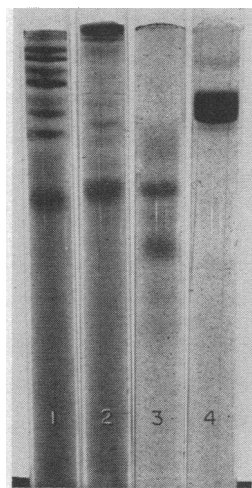

FIGURE 4 Disc electrophoresis on polyacrylamide gel of IgA isolated from serum of patient (1) and (2) and from IgA myeloma serum (3) and (4). Treatment of isolated IgA: (2) and (4) with 1% SDS, 0.05 M urea in 0.05 M phosphate buffer, pH 7.1; (1) and (3) reduced with 0.1% 2-ME in 0.05 M phosphate buffer, pH 7.1 10% acetic acid, 1% SDS, 0.5 M urea. Electrophoresis was carried out in 0.1 M phosphate buffer, pH 7.1, and 0.1% SDS for 150 min at 15 ma/tube. Lower band in (1) and (2) correspond to slow moving α-chain of IgA myeloma in (3); fast moving band in (3) represents light-chain. Note absence of light-chain in (1). Main band in (4) represents nonreduced 7 S IgA. Concentration of both patient's and myeloma IgA was 1%. Anode is at the bottom of the figure.
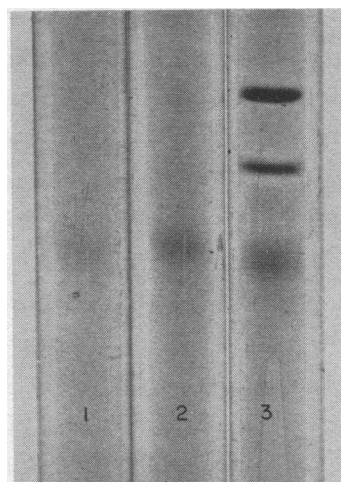

FIGURE 6 Disc electrophoresis on polyacrylamide gel of urinary IgA (fraction I from Sephadex G-200). Reduction, SDS-treatment, and electrophoresis as in Fig. 5. (1) patient's reduced IgA; (2) patient's nonreduced IgA; (3) Bence Jones protein (light-chain dimer, lower band) from myeloma patient, nonreduced.

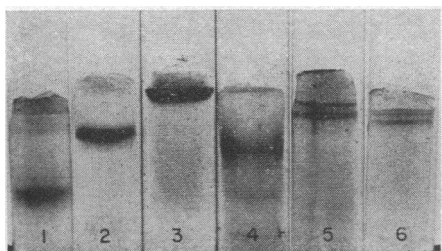*Absence of Light-Chain–α-Chain Assembly*   2729

FIGURE 7 Disc electrophoresis on polyacrylamide gel of isolated IgA from saliva of family members. Electrophoresis was carried out in 0.005 M Tris—0.0384 M glycine—HCl, pH 8.6, for 90 min at 4 ma/tube. (1) proposita's elder son; (2) proposita; (3) proposita's husband; (4) proposita's mother; (5) proposita's father; (6) normal control.

her mother's saliva contained a considerable amount of IgG, the ratio α-chain:IgG in the proposita being 9:1, in her mother 2.5:1, in her elder son 15:1. In both proposita's mother and elder son the urine contained free α-chains and free light-chains. The urines of the other family members were not examined. Serum could be obtained only from the proposita's husband and elder son; the former contained normally assembled IgA, while in the latter free α-chains were found.

Characterization of tonsillar nascent immunoglobulins

Biosynthesis of immunoglobulins in the proposita's tonsillar cells in short-term culture and secretion of immunoglobulins by the cells into the culture medium was studied by using amino acids-^{14}C as described in Methods.

Cell lysate. The immune precipitates obtained with specific antisera from patient's tonsillar cell lysate were dissolved, reduced, and run on acrylamide gel (Fig. 8). Electrophoresis of the reduced isolated IgM and of the reduced isolated IgG revealed for each two radioactive peaks migrating similarly to reduced heavy- and light-chains derived from normal serum. The reduced isolated IgA obtained from the cell lysate showed a major peak corresponding to normal serum heavy-chain markers as well as to the heavy-chain obtained from patient's tonsillar IgG; the radioactivity corresponding to the light-chain peak was significantly less than normal.

Since the precipitated tonsillar IgA appeared to contain few or no covalently bound light-chains, the latter were searched for in the supernatant of patient's tonsillar cell lysate precipitated successively with anti-γ-chain serum, anti-μ-chain serum and anti-α-chain serum. The supernatant was reacted with goat anti-human light-chain serum, the precipitate dissolved, reduced, and run on acrylamide gel. As seen in Fig. 8 a large peak was obtained with location corresponding to that of the light-chain markers derived from patient's ton-

sillar IgG and IgM, as well as to that of a normal serum light-chain marker. When the same procedure was applied to the cell lysate from the control patients, no free light-chains were found in the cell lysate after immune precipitation of IgG, IgM, and IgA. The specifically precipitated IgA contained both heavy- and light-chains (Fig. 9).

DISCUSSION

Thus far three types of immunoglobulin disorders characterized by the presence of heavy-chain fragments in the serum and urine have been described, γ-heavy-chain disease (26), α-chain disease (2), and μ-chain disease (27, 28). In γ- and α-chain diseases the proliferating cells produce abnormal heavy-chains but no
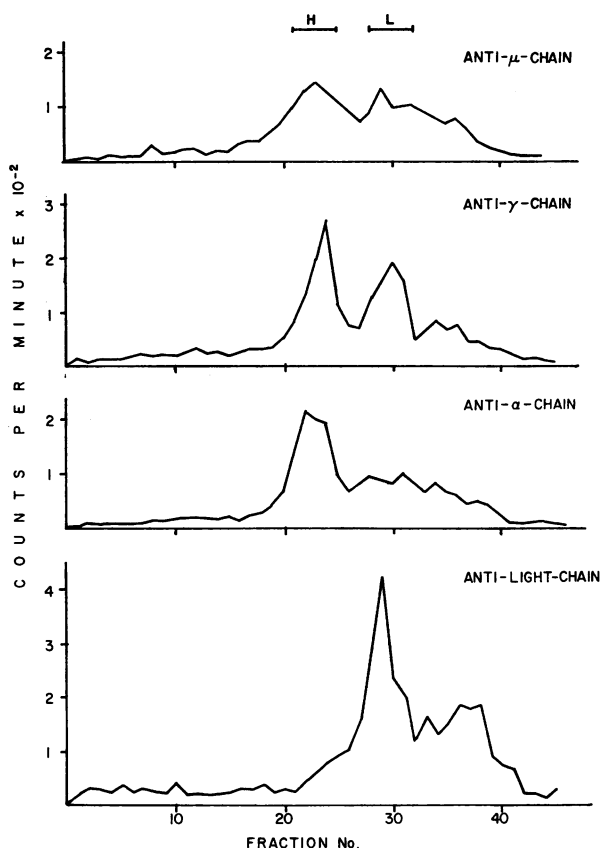

FIGURE 8 Disc electrophoresis on polyacrylamide gel of isolated nascent immunoglobulins successively (top to bottom) precipitated from patient's tonsillar cell lysate with specific anti-heavy-chain sera. The light-chains were precipitated from the final supernatant with goat anti-human light-chain serum. Each of the precipitated immunoglobulins was reduced with 0.1% 2-ME in 0.05 M phosphate buffer, pH 7.1, 10% acetic acid, 1% SDS, 0.5 M urea. Electrophoresis was carried out in 0.1 M phosphate buffer, pH 7.1 and 0.1% SDS for 150 min at 15 ma/tube. H and L represent heavy- and light-chain markers.

light-chains, as demonstrated in bone marrow (29) and intestinal biopsy material (2), while in μ-chain disease both heavy- and light-chains appear to be produced but fail to be assembled into the IgM molecule (27). The presently described immunoglobulin A abnormality differs from the previously reported cases of α-chain disease in that the abnormal immunoglobulin-producing cells synthesize both α-chain and light-chains, but do not assemble them. Clinically, this immunoglobulin A abnormality is clearly distinct from α-chain disease, in that it is an hereditary disorder without evidence of malignant lymphoma or malabsorption, but is associated with recurrent upper respiratory tract infection and tonsillitis.

The study of nascent immunoglobulin synthesis in the patient's tonsillar cells maintained in short-term culture demonstrated that both α-chains and light-chains were produced but not assembled, and that the cells were able to secrete both the free α-chains and the free light-chains. The presence of the IgA abnormality in patient's serum and saliva and the persistence of the abnormality after tonsillectomy indicate that the defect in immunoglobulin assembly, demonstrated in the tonsillar cells, represents a general abnormality of the IgA-producing cells in the body. Indeed, Crabbé and Heremans (30) have shown that the nasopharyngeal tonsils in the human resemble the lymph nodes and spleen regarding the frequency distribution of plasma cells, producing immunoglobulins of the various subclasses. Whereas in our patient the secretion by IgA-producing cells of free α-chains was reflected by their presence in the serum, saliva, and urine, secretion of free light-chains was manifest only in their presence in high concentration in patient's urine. The inability to demonstrate free light-chains in patient's serum may be explained by their rapid clearance (31). The elution pattern of urinary α-chains and light-chains from Sephadex G-200 revealed that most of the α-chains and most of the light-chains were in polymerized form. The separate γ-chain and light-chain peaks obtained suggest that the polypeptide chains were excreted in the urine nonassembled, and polymerized separately. The separate urinary secretion of the α-chains and light-chains furnishes additional evidence for their presence in serum in nonassembled form. In contrast, in μ-chain disease there is evidence for intracellular polymerization of the heavy-chain (27), which, indeed, could explain the nonexcretion of μ-chain from the blood stream into the urine.

Since the IgG and IgM synthetized in patient's tonsillar cells as well as the IgG and IgM found in the patient's serum contained assembled light- and heavy-chains, it is reasonable to assume that the primary defect resulting in nonassembly of light- and α-chains,
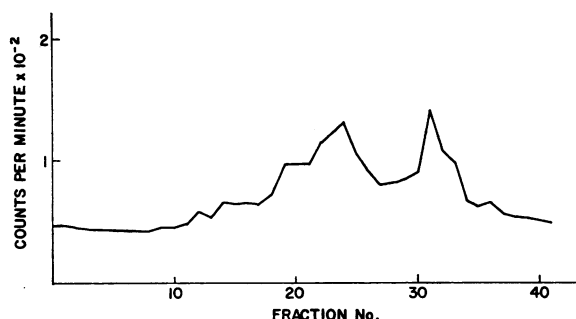

FIGURE 9 Disc electrophoresis on polyacrylamide gel of isolated nascent IgA precipitated with anti-α-chain serum from tonsillar cell lysate of control patient. The precipitated IgA was reduced with 0.1% 2-ME in 0.05 M phosphate buffer, pH 7.1, 10% acetic acid, 1% SDS, 0.5 M urea. Electrophoresis was carried out in 0.1 M phosphate buffer, pH 7.1 and 0.1% SDS for 150 min at 15 ma/tube.

is in the α-chain. Structural and chemical studies in γ-heavy-chain (26, 32) and α-chain disease (33) have revealed that the heavy chains represented mainly the Fc fragment of the γ-chain or α-chain. The molecular weight of our patient's free α-chain has not been determined. However, the electrophoretic mobility of the reduced nascent free α-chain, isolated from the patient's tonsillar cells on acrylamide gel in SDS and urea, was similar to that of a normal α-chain, suggesting a similar molecular weight. Since the electrophoretic migration on acrylamide gel electrophoresis in SDS of the serum and urinary alpha-chain monomers corresponded to that of a IgA myeloma α-chain and a light-chain dimer, respectively, the molecular weight of the α-chain appears to be around 50,000.

Patient's saliva was remarkable in that it contained α-chain linked to secretory piece but no light-chains. Lack of light-chains in patient's secretory IgA, rather than it possessing "hidden" light-chain determinant as has been described for some IgG (34) and IgD (35) immunoglobulins, was evidenced by failure of the isolated salivary IgA to react with anti-light-chain sera type K or type L even after reduction and alkylation. In α-chain disease the saliva, though containing normal IgA, may be devoid of or contain free α-chain, as reported by Seligmann, E. Mihaesco, Hurez, C. Mihaesco, Preud'homme, and Rambaud (33), α-chain linked to SP was found by these authors in the urine of two of their patients with α-chain disease (33). The finding in our patient's saliva of α-chains linked to SP supports Tomasi's and Bienenstock's (36) assumption of heavy-chain–SP linkage in secretory IgA.

The relationship between patient's recurrent tonsillitis and her IgA abnormality is unclear. Absence of secretory IgA from saliva in hypogammaglobulinemia-A has been invoked to explain lack of local defense

mechanisms (37). It is interesting to speculate that incomplete secretory IgA, consisting of α-chain and SP but lacking light-chain, has ineffective antibody function. Tomasi (38) has reported the compensatory secretion of IgM into the saliva in children with no secretory or serum IgA, this secretory IgM being active against some bacteria. No IgM, however, could be detected in the saliva of our patient. It may be relevant that the proposita's mother, who did not suffer from upper respiratory infections although her salivary IgA lacked light-chain, had a considerable amount of IgG in her saliva.

The nature of the mutation causing the immunoglobulin A abnormality in this family has not been clarified. The finding that on acrylamide gel electrophoresis both reduced and nonreduced, but SDS-treated, serum as well as urinary α-chains migrated identically, indicates that the α-chains are not covalently bound by S-S bonds. Typing of the salivary, serum, and urinary IgA was done by Dr. E. Franklin, who found it to be of the A₁ subclass, in which normally the light- and heavy-chain are covalently bound (39).

Immunoglobulin studies carried out thus far in this family showed the IgA abnormality to be present in three generations. Genetic studies concerning the mode of inheritance of this new mutation in this family are in progress.

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