Kappa-Chain Deficiency

By George M. Bernier, J. Richard Gunderman, and Frederick B. Ruymann

A decreased concentration of immunoglobulin molecules of one light chain type (κ) was found in a young girl with recurrent respiratory infections and diarrhea. She had, in addition, decreased γA and γE globulin, partial albinism, and intestinal lactase deficiency. No eosinophils were detected in blood, bone marrow, or nasal smears. Radiolabeled κ- and λ-type molecules survived equally well, suggesting that the synthesis of molecules bearing κ-chains was decreased. The patient improved considerably with the regular administration of γ-globulin. It is possible that biological as well as chemical differences exist between immunoglobulins of the two light-chain types and that an optimal immune response is dependent on a normal complement of κ- and λ-chains.

Increased Susceptibility to pyogenic infections has been a common manifestation of immunoglobulin deficiency. In patients with frequent infections, the degree of immunoglobulin deficiency has been variable in that some patients exhibit extreme depression of all immunoglobulin classes and others are deficient in only a single class. In some patients with recurrent infections, decreased concentration of even one or two subclasses of γG globulin has been implicated. Class and subclass distinctions of immunoglobulins are based on differences in heavy chains, and immune disorders attendant on deficiencies of a class or subclass have been taken as presumptive evidence for the biological importance of the deficient class or subclass. Immunoglobulins also differ by virtue of their light chains (κ and λ), and selective deficiency of one or the other light chain might be expected to result in compromised humoral immunity. However, to date, deficiency of immunoglobulins of a single light-chain type has not been described. This report concerns a young girl with repeated respiratory infections and diarrhea whose serum and secretory immunoglobulins were found to have a selective deficiency of κ-type molecules. The survival of administered γ-globulin was normal with respect to both light-chain types, suggesting that κ-chain synthesis was selectively suppressed.

Case Report

The patient, N.C., was a full-term baby, the product of a consanguineous (uncle-niece) marriage. She had normal growth and development, but from her earliest days, was a

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“spitter” and had frequent loose bowel movements. At the age of 11 mo she was admitted to another hospital for the first time with bronchitis, dehydration, and diarrhea. Serum immunoglobulin levels measured at that time were γG 2.8, γA 0.6, and γM 0.5 mg/ml. During the next 2 yr, she required multiple hospital admissions and received frequent antibiotic treatment for otitis media, pneumonia, and bronchitis. The infections were considered to be bacterial, since they were associated with polymorphonuclear leukocytosis and fever, and responded to penicillin. She was treated episodically with γ-globulin. At the age of 3 yr 6 mo when the peculiar immunoglobulin abnormality described herein was appreciated, she was begun on intramuscular γ-globulin (5 ml every other week) and in the intervening 2 yr the patient has not had any serious respiratory or sinus infections. The diarrhea has at various times been partially relieved by fat restriction, gluten restriction, and lactose restriction. It has not been helped at all by the oral administration of oxytetracycline or preparations of pancreatic enzymes.

There was a family history of asthma, heart disease, carcinoma, and arthritis. The patient’s mother had a mild form of sero-negative arthritis beginning at age 28, and the patient’s father died at 41 of carcinoma of the lung. The patient’s maternal grandmother, who was simultaneously the patient’s paternal aunt, also had arthritis. There was no history of albinism, recurrent infection, or hematologic malignancy.

The patient’s appearance was striking with white hair, extremely long white eyelashes, and very pale skin. The albinism was partial, however, as there was brown pigmentation of the iris. The remainder of her physical examination (when she had no respiratory infection) was unremarkable; significantly absent were lymphadenopathy, splenomegaly, evidence of chronic monilial infection, ataxia, and telangiectasia.

Chest x-rays at 11 mo showed a thymus shadow, but at age 3 yr, x-ray films demonstrated a paucity of nasopharyngeal lymphoid tissue.

MATERIALS AND METHODS

Studies of the patient’s immunoglobulin concentrations reported here were performed at age 3 yr, 5 mo when she had not received exogenous γ-globulin for several months. Quantitative estimations of serum immunoglobulins G, A, and M levels were made using Hyland Immunoplates. Serum levels of γD globulin were also measured by the Mancini method, using rabbit anti-γD prepared by immunization with a γD myeloma protein. Immunoelectrophoresis was on microscope slides using the agar gel electrophoresis system of Wieme. Horse anti-whole human serum was obtained commercially from the Netherlands Red Cross. Specific antisera to γ, α, μ, δ, κ, and λ chains were raised in rabbits by immunization by monoclonal immunoglobulins or isolated chains. All antisera were appropriately absorbed.

The κ/λ ratio was determined quantitatively by radial diffusion in agar. Plates were prepared containing either anti-κ or anti-λ antiserum incorporated in the agar. Diluted serum samples were added to wells, 3 mm in diameter. The areas of the resultant rings were measured as previously described. The standards employed were serial dilutions of a Lot of Human γ Globulin (Hyland). The κ/λ ratio of the standard was determined by trace labeling the γ-globulin with 125I and measuring the relative amounts of radioactivity precipitated by anti-κ antiserum and by anti-λ antiserum at equivalence.

The patient’s γM and γG globulin fractions were separated by gel filtration using 1 ml of serum (Sephadex G-200, 0.15 M NaCl, 30 × 2.5 cm column). Those fractions free of cross contamination were concentrated and the κ/λ ratio was determined by radial diffusion. The survival of exogenous γ-globulin in the patient was studied at 3 yr, 9 mo of age following intramuscular injection of 2 mg γ-globulin labeled with 3 μCi 125I. The patient received Lugol’s solution before and for 2 mo after injection. The γ-globulin (Cohn fraction 2 for human use, Hyland) was labeled by the chloramine-T method described by McConahey and Dixon, using carrier-free radionuclide. The labeled γ-globulin was dialyzed for 36 hr against physiologic saline in the cold and was sterilized by passage through a 0.54 μ Millipore filter. Serum samples were obtained at intervals during the succeeding
41 days. The radioactivity of whole serum, of the fraction precipitated by anti-κ antiserum, and of the fraction precipitated by anti-λ antiserum was measured in a γ-detector (Nuclear Chicago). The precipitates were prepared by reacting 1.0 ml serum with 10 ml anti-κ or anti-λ antiserum for 1 hr at 37°C. The reactants stood at 0°C overnight, were centrifuged at 10,000 rpm, washed three times in chilled saline, and dissolved in 1 N NaOH.

Concern over the possibility of anaphylaxis prompted the intramuscular, rather than intravenous, route of administration of the labeled γ-globulin.

Sensitization to dinitrochlorobenzene (DNCB) was performed as described by Brown et al.9 Small intestinal biopsy was performed with a Crosby capsule. Tissue was examined by light and electron microscopy and was stained with fluorescent antibodies to γG, γA, γM, κ, λ, and C3. Tissue was assayed for various disaccharidases.10

RESULTS

Immunoglobulins

Immunoelectrophoresis of the child’s serum provided the first evidence that her immunoglobulins were deranged in a unique way. A double arc was present in the γG region, and γA globulin was not detected. As demonstrated in Fig. 1, the second γG arc was the consequence of selective reduction of immunoglobulins bearing κ-light chains. As measured by radial diffusion (Fig. 2) the κ/λ ratios of whole serum, of γM, of γG, and of concentrated saliva were all reduced.

The urinary κ/λ ratio was much higher than serum but was still less than the urinary κ/λ ratios of healthy controls. The radial diffusion technique measures molar concentrations of antigens. Since free κ-chains tend to exist as monomers and free λ-chains as dimers,11,12 the molar ratio of free κ- and λ-chains would be significantly higher than the ratio of concentrations expressed in mg/ml. Since the light chains in urine are predominantly free, the apparent κ/λ ratio would be expected to be higher than that of serum.

Serum concentrations of γG, γA, γM, and γD, and κ/λ ratios were measured on six different occasions between age 3 and 4½. The values given in Table 1 are representative: the patient’s serum levels of γA and γE globulin were decreased, γA globulin was not detected in the patient’s saliva, but secretory component, γM and γG globulin were present. No monoclonal immunoglobulin was detected by agar gel electrophoresis or immunoelectrophoresis. As judged by Ouchterlony analysis of the fractions obtained by filtration of the patient’s serum through Sephadex G-200, free light chains were not present in the patient’s serum in significant amounts.

Survival of exogenous γ-globulin was studied to distinguish between decreased production of κ-type molecules and their increased destruction as alternate possibilities. The slope of the biological decay curve (t½=21 days) was similar to that obtained by administration of labeled γ-globulin intravenously to normal individuals,13 although the initial part of the survival curve was decidedly different as would be expected from intramuscular administration. A constant ratio was observed between the radioactivity precipitated by anti-κ, by anti-λ, and whole serum (Fig. 3). The radioactive κ/λ ratio of serum at each point in time was virtually identical to the radioactive κ/λ ratio of the original pool of radiolabeled γ-globulin. The amount of protein precipitated from the patient’s serum by anti-λ was always greater
Fig. 1. (Top). Immunoelectrophoresis of patient's serum (upper well) and of normal serum (lower well), developed with horse antihuman serum. Anode at right. A double γG arc was present in patient's serum. (Bottom). Immunoelectrophoresis of patient's serum (upper and lower wells), developed as above. After electrophoresis, a drop of free κ-chains was placed on agar at cathodal end of upper electrophoretic path. κ-chains produced an arc with antiserum that fused with inner γG globulin arc. This demonstrated that inner arc of patient's γ-globulin was produced by reaction of her κ-type molecules and horse anti-κ antibodies that had diffused past γG molecules lacking κ-chains. In normal serum, κ-type molecules were in relative excess, and a double arc did not occur.
Immunoglobulin levels were normal in family members surveyed, except for the patient's serum. The sum of the radioactivities precipitated by anti-\( \kappa \) and anti-\( \lambda \) approached that of whole serum, ranging from 87% to 90% at any point. The survival study, therefore, was consistent with decreased \( \kappa \)-chain synthesis.

The patient was blood group 0. Anti-A and anti-B isoagglutinins were detected with immune anti-A present at 1:16. The Schick test was twice positive, once following a DPT booster. Antibodies to bovida antigens\(^{14} \) were not detected. The specimen obtained by intestinal biopsy did not contain any cells that stained with fluorescent antibodies to C3 or the \( \gamma^+ \), \( \alpha^- \), \( \mu^- \), \( \kappa^- \), or \( \lambda^- \)-chains. The bone marrow specimen, which contained plasma cells, was not examined with these reagents.

**Cellular Immunity**

Delayed skin reactions failed to develop when the patient was challenged with monilia, streptokinase-streptodornase (SKSD), trichophytin, PPD, histoplasmin, and mumps antigens. However, she reacted normally to DNCB following sensitization. Lymphocyte transformation was not studied.

**Immediate Reactivity**

The patient did not react to any of 30 common allergens applied as scratch tests to the skin.

**Eosinophils**

No eosinophils (or eosinophil precursors) were detected in the child's peripheral blood, in her nasal secretions, in the intestinal biopsy, or in the aspirate of her bone marrow. The absence appeared to be of relatively late onset, since levels as high as 16% eosinophils had been detected in differential counts of peripheral blood at age 11 mo. However, for the year preceding the studies described herein, no eosinophils had been noted in differential blood counts.

**Family Studies**

Immunoglobulin levels were normal in family members surveyed, except
Table 1. Immunoglobulin Concentrations of Patient's Serum and $\kappa/\lambda$ Ratios of Various Body Fluids at 3 Yr, 9 Mo

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>Serum immunoglobulin level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma$G globulin</td>
<td>9.10 mg/ml</td>
<td>6.5-14.0 mg/ml</td>
</tr>
<tr>
<td>$\gamma$A globulin</td>
<td>0.15 mg/ml</td>
<td>1.0-3.5 mg/ml</td>
</tr>
<tr>
<td>$\gamma$M globulin</td>
<td>1.00 mg/ml</td>
<td>0.4-1.6 mg/ml</td>
</tr>
<tr>
<td>$\gamma$D globulin</td>
<td>&lt;5.0 mcg/ml</td>
<td>&lt;5.0-300 mcg/ml</td>
</tr>
<tr>
<td>$\gamma$E globulin</td>
<td>20 ng/ml</td>
<td>100-700 ng/ml</td>
</tr>
<tr>
<td>$\kappa/\lambda$ ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>0.66</td>
<td>1.5-2.1*</td>
</tr>
<tr>
<td>$\gamma$G fraction</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>$\gamma$M fraction</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Saliva</td>
<td>0.60</td>
<td>1.76-1.90†</td>
</tr>
<tr>
<td>Urine</td>
<td>1.5</td>
<td>2.3-2.7†</td>
</tr>
</tbody>
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*Range of 30 normal blood donors.
†Range of three normal concentrates.

for the patient's maternal grandfather whose $\gamma$M was decreased with a high $\gamma$G and slightly increased $\gamma$A (Table 2). The $\kappa/\lambda$ ratios of some family members were slightly lower than the normal range, and curiously, the ratio was consistently at the upper limits of normal in the patient's only sister, age 11.

**Intestinal Studies**

Light microscopy of the jejunal biopsy showed a mild decrease in villus height with shortened columnar epithelial cells. Increased lymphocytic infiltration of the lamina propria was present with a large lymphoid nodule within the lamina propria. Methylpyronine and PAS stains showed normal numbers of goblet cells, but plasma cells were not identified. Tissue levels of maltase, sucrase, and cellobiase were normal, and the lactase level (61.4 U/g protein) was low. Serum $B_{12}$ was normal (240 pg/ml); serum and red cell folate were increased (21.2 and 653 ng/ml, respectively). Stool examinations showed increased fat, no ova, parasites, or enteric pathogens. *Giardia lamblia* was specifically searched for and not identified.

**Other Studies**

Urine excretion of amino nitrogen was normal on two occasions (79 and 48 mg amino nitrogen/24 hr). Chromosomal karyotype was 46, XX. No abnormal granulations were seen in the patient's granulocytes. Hematocrit was 34%, white blood count was 15,500/cu mm, and platelets were 365,000/cu mm. Differential smear showed 63% segmented neutrophils, 1% bands, 1% basophils, 32% lymphocytes, 3% monocytes, 0 eosinophils. Bone marrow aspirate showed a myeloid-erythroid ratio 3.5, and increased size of meta-myelocytes was noted, consistent with a mild megaloblastic process.
KAPPA-CHAIN DEFICIENCY

801

DISCUSSION

Deficiency of immunoglobulins of a single light-chain type represents a new kind of immune defect. Because the child had several other abnormalities of the immune system, the importance of κ-chain deficiency was difficult to assess. The light-chain aberration did, however, result in a marked disturbance of normal immunoglobulin relationships. Normally, immunoglobulin molecules containing κ-light chains are present at approximately twice the concentration of molecules containing λ-light chains.18 Sera of normal individuals contain on the average 12 mg/ml γG globulin, of which 7.7 mg are γ2 κs and 4.3 mg γ2 λs. Our patient’s serum contained 9.6 mg γG globulin, of which only 3.8 mg were γ2 κs. The γ2 λs molecules were present at a concentration somewhat higher than normal, 5.8 mg/ml.

Differences in chemical composition16,17 and in tendency to polymerize11,12,18 are known to exist between the two species of light chains. Physiologic differences are unknown but presumably exist.

Grey and Mannik have demonstrated the selective affinity of light and heavy chains of individual myeloma proteins for each other.19 By analogy, in the formulation of antibody molecules, some heavy chains presumably require specific light chains for optimal function. If the potential pool of

![Graph](image-url)

Fig. 3. Survival curve of 125I-labeled γ-globulin injected intramuscularly, expressed as cpm/ml of whole serum (black circles) and as cpm precipitated from 1 ml of serum by anti-κ (open circles), and by anti-λ (open squares). Values obtained 12 hr after injection are slightly less than 4-day values, implying gradual equilibrium between extravascular and intravascular pools. Survival curves are parallel, indicating similar catabolic rate of both species of γ-globulin.
\(\kappa\)-chains were decreased, as it was in our patient, those antibodies dependent on specific \(\kappa\)-chains would be expected to be less effective with substituted \(\lambda\)-chains.

Variation in \(\kappa/\lambda\) ratios has been previously noted. In the study of a large series of hypogammaglobulinemic individuals, Yount et al.\(^{20}\) found in some, variation in the relative concentrations of \(\gamma\)G subclasses and of \(\kappa/\lambda\) ratios. The individuals studied differed from our patient in three important ways: all were hypogammaglobulinemic with serum \(\gamma\)G concentrations less than 6 mg/ml, the lowest \(\kappa/\lambda\) ratio recorded in that study was 0.9, and all had deficiency of both \(\kappa\)- and \(\lambda\)-type molecules.

Two lines of information suggest that the light-chain imbalance contributed to the child’s infectious problems. Humoral antibody was deficient as judged by Schick testing on two occasions, and the regular administration of \(\gamma\)-globulin resulted in a marked decrease of infections. However, she had abnormalities also in \(\gamma\)A and \(\gamma\)E globulin, in eosinophils, and in absorption.

Deficiency of \(\gamma\)A and \(\gamma\)E globulin has often been associated with sino-pulmonary infection and diarrhea.\(^{21}\) However, approximately one in 500 normal individuals has a total lack of \(\gamma\)A globulin,\(^{22}\) and \(\gamma\)E globulin absence has been described in an otherwise normal individual.\(^{23}\) Thus, the patient’s susceptibility to infection may or may not have been a reflection of secretory \(\gamma\)A and \(\gamma\)E deficiency.

Eosinophils are clearly related to some aspects of the immune response,\(^{24}\) and clinically, eosinophilia is a common accompaniment of allergic states. Apparent complete absence of eosinophils must be very rare, as we have found only two cases of an eosinophilia described.\(^{25,26}\) Both patients had allergic conditions, and in one case\(^{28}\) consanguinity was present. The lack of eosinophils in our patient was an acquired trait, since increased levels were detected.

| Table 2. Immunoglobulin Levels (mg/ml), \(\kappa/\lambda\) Ratios of Family Members* |
|-----------------|--------|--------|--------|-----------------|
| Patient’s sister—age 11 | \(\gamma^G\) | \(\gamma^A\) | \(\gamma^M\) | \(\kappa/\lambda\) |
| Patient’s mother | 12.6 | 1.9 | 1.56 | 1.4† |
| Mother’s parents | | | | |
| Mother | 11.5 | 2.3 | 0.90 | 1.5 |
| Father | 19.0† | 4.1† | 0.17† | 1.7 |
| Mother’s sibs | | | | |
| Brother | 11.5 | 4.0† | 0.56 | 1.9 |
| Sister | 14.2 | 3.0 | 0.64 | 1.5 |
| Sister | 11.5 | 2.1 | 1.45 | 1.5 |
| Father’s sibs | | | | |
| Brother | 13.8 | 2.7 | 1.23 | 1.4 |
| Brother | 8.6 | 3.1 | 0.64 | 1.5 |
| Sister | 11.5 | 2.3 | 1.09 | 1.3† |
| Sister | 16.2† | 3.8† | 1.23 | 1.6 |
| Sister | 11.5 | 2.2 | 0.64 | 1.4† |

* All relatives are over 20 yr of age, except the patient’s sister, age 11.
† Values outside normal range.
several times during her first 2 yr. Whether the absence of eosinophils contributed to her problems or whether it was in some way a consequence of infection, γ-globulin injections, the light-chain imbalance, or her peculiar pigmentation is unknown.

Malabsorption, sometimes with lactase deficiency, has been described with some frequency in patients with humoral and/or secretory immune deficiency. The importance of this to our patient is also uncertain.

The testing with DNCB clearly established that the patient was capable of delayed hypersensitivity. However, her failure to react to any of the four common antigens used is difficult to explain readily. The possibility exists that the thymic-dependent system was to some degree impaired, and this, too, may have contributed to her propensity for infection. She was receiving exogenous γ-globulin at the time of skin testing. It is unlikely but possible that administered humoral antibodies interfered with the delayed skin reactivity.

The mechanism of decreased κ-chain production (and apparent compensatory λ-chain hyperproduction) is obscure. Several possible genetic mechanisms might be implicated. The child was the product of a consanguineous marriage. This would favor an autosomal recessive inheritance pattern. However, it was not possible to identify clearly heterozygotes in her kindred.

The number of κ-molecules in the patient’s serum was approximately one-half normal; hence, the possibility existed that one structural κ-chain gene had been somehow deleted, and the immunoglobulin synthesized was the product of the remaining gene. The sera of the patient and her family were typed according to the genetic marker (Inv) associated with the κ-light chain. Gene deletion would have been excluded by the presence in the patient of two alleles for this genetic locus. However, the patient and all the members of her kindred shown in Table 2 were Inv (−1, −2, +3), compatible with the genotype Inv 3/3. Since the patient’s father could not be tested, information is not complete. The patient could, of course, have the genotype Inv 0/3, but this was not testable.

The basic defect might theoretically be a transcriptional error in the κ-chain, involving the region of the interchain disulfide bond, preventing linkage to heavy chains. This kind of abnormality has been shown to exist in some cases of heavy-chain disease. If this were the mechanism, we would anticipate that excessive free κ-chains would be detected in the urine. As shown in Table 1, the κ/λ ratio of urinary light chains was abnormally low.

The findings in this patient provide yet another way in which the complexities of the immune system may be deranged and raise the question of the qualitative and quantitative importance of light chains in immune deficiency states.

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REFERENCES

KAPPA-CHAIN DEFICIENCY


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