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Immunoglobulin K light chain deficiency: A rare, but probably underestimated, humoral immune defect

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ABSTRACT

Human immunoglobulin molecules are generated by a pair of identical heavy chains, which identify the immunoglobulin class, and a pair of identical light chains, Kappa or Lambda alternatively, which characterize the immunoglobulin type. In normal conditions, Kappa light chains represent approximately 2/3 of the light chains of total immunoglobulins, both circulating and lymphocyte surface bound. Very few cases of immunoglobulin Kappa or Lambda light chain defects have been reported. Furthermore, the genetic basis of this defect has been extensively explored only in a single case.

We report a case of a patient suffering of serious recurrent bacterial infections, which was caused by a very rare form of immunoglobulin disorder, consisting of a pure defect of Kappa light chain. We evaluated major serum immunoglobulin concentrations, as well as total and free Kappa and Lambda light chain concentrations. Lymphocyte phenotyping was also performed and finally we tested the Kappa chain VJ rearrangement as well as the constant Kappa region sequence.

Studies performed on VJ rearrangement showed a polyclonal genetic arrangement, whereas the gene sequencing for the constant region of Kappa chain showed a homozygous T to G substitution at the position 1288 (rs200765148). This mutation causes a substitution from Cys to Gly in the protein sequence and, therefore, determines the abnormal folding of the constant region of Kappa chain. We suggest that this defect could lead to an effective reduction of the variability of total antibody repertoire and a consequent defect of an apparently normal immunoglobulin response to common antigens.

1. Introduction

Human immunoglobulin molecules are built up by a pair of identical heavy chains, identifying the immunoglobulin class (namely Gamma, Alpha, Mu, Delta and Epsilon), and by a pair of identical light chains, Kappa or Lambda alternatively, characterizing the immunoglobulin type. In humans, under normal conditions, Kappa light chains represent approximately 2/3 of the light chains of total immunoglobulins, both circulating and lymphocyte surface bound. Since the first report in 1972 [Bernier et al., 1972], very few patients with immunoglobulin Kappa or Lambda light chain defects have been reported; therefore, the clinical impact and the prevalence of this defect remain yet undefined. Furthermore, the genetic basis of this defect has been identified in a single case only [Stavnezer-Nordgren et al., 1985]. Here we report a patient with total Kappa light chain deficiency. Such a defect was occasionally detected in a 62 year old female suffering from very early age of recurrent respiratory infections and intestinal disorders.

2. Case report and genetic analysis

The patient, a 62 year-old woman, offspring of non-consanguineous parents and native from Campania (South Italy), was firstly observed in the course of a laboratory workup for the search of monoclonal components and subsequent secondary

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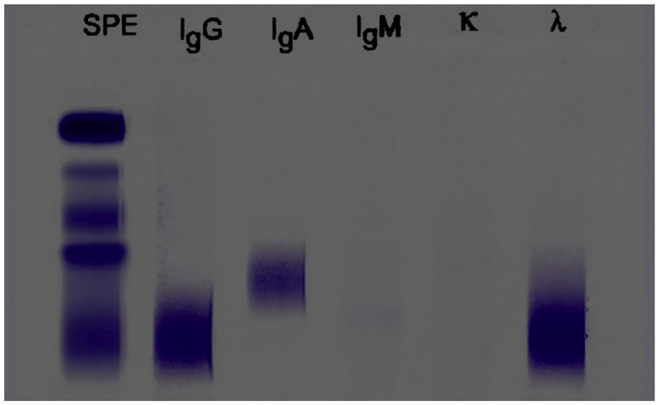

Fig. 1. Immunofixation Electrophoresis of patient's serum. From left to the right: reference electrophoresis, anti IgG, anti IgA, anti IgM, anti Kappa, anti Lambda. Note the total absence of reactivity in the anti Kappa lane and the strong reactivity with anti Lambda.

leading to respiratory insufficiency. Thus, she underwent several hospitalizations and continuous aggressive antibiotic therapy. The patient was also affected by recurrent episodes of not well defined diarrhea. The search for monoclonal immunoglobulins resulted negative. However, the absence of reactivity in the lane of anti Kappa antiserum was noted (Fig. 1). The total absence of reactivity was confirmed by a repeated test. Moreover, a nephelometric evaluation of total (bound and free) Kappa and Lambda light chains demonstrated a total absence of Kappa and a significant increase of Lambda light chains. A similar result was found for free Kappa and Lambda light chains. Immunoglobulin IgG, IgA, IgM, IgE and IgD subclasses showed normal concentrations. Lymphocyte phenotyping showed an almost total absence of Kappa light chain in B cells. Studies for the VJ rearrangement showed a polyclonal genetic arrangement, thus excluding B lambda cell clonal expansion. All B lymphocytes resulted positive for surface Lambda type immunoglobulins (Fig. 2). All patient's laboratory data are summarized in Table 1.

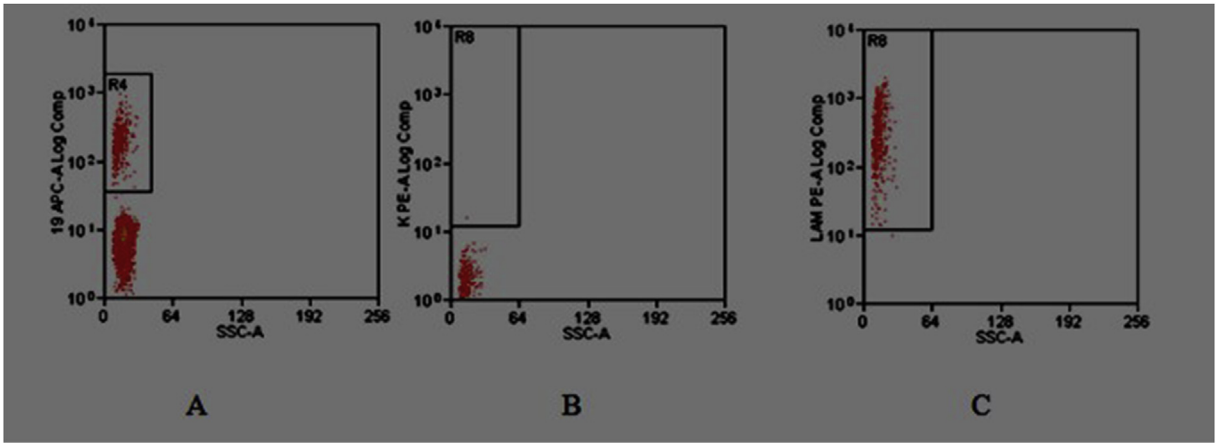

Fig. 2. Expression of surface Kappa and Lambda Immunoglobulin light chains in the peripheral blood by flow cytometry. Lymphocytes were gated using the CD45/SSC dot-plot and CD19+ (gate R4) B-cells were studied for expression of Kappa and Lambda Immunoglobulin light chains (A). B) Gated on R4. Dot-plot representing the almost total absence of surface Kappa light chain expression C) Gated on R4. Dot-plot showing strong expression of lambda light chain. For each sample isotype matched antibodies were used as negative control.

Table 1
Essential laboratory test in the patient and her relatives.

Test	Patient	Mother	Daughter	REF. Values
Total serum K chains	n. d.	2.55	1.93	1.70–370 g/L
Total serum λ chains	5.50	2.10	1.40	0.99–2.0 g/L
Free serum K chains	n. d.	19.1	8.4	3.3–19.4 mg/L
Free serum λ chains	65.9	50.5	15.7	5.7–26.3 mg/L
Serum IgG	14.90	12.10	9.23	7.40–14.40 g/L
Serum IgA	3.06	3.20	1.13	0.140–4.00 g/L
Serum IgM	1.21	0.91	0.74	0.65–0.2.10 g/L
Serum IgG 1	10.90	8.40	6.00	4.05–10.11 g/L
Serum IgG 2	3.39	2.55	1.95	1.69–7.86 g/L
Serum IgG 3	0.70	0.11	0.12	0.11–0.85 g/L
Serum IgG 4	0.16	0.20	0.18	0.03–2.01 g/L
Total serum IgE	50.1	77.5	41.1	1.5–100 kIU/L
Total peripheral blood lymphocytes	1152.5	2233.3	1320.2	1.0–4.0 μL
B peripheral blood lymphocytes (CD19+)	184.2	402.3	211.2	105–560/μL
CD19 + K + lymphocytes	0.23	268	79	63–336/μL
CD19+λ+lymphocytes	183	134	132	42–224/μL
Lymphocyte k/λ ratio	0.01	2.0	0.6	0.6–3.0

n. d. = not detectable.

immunodeficiency in a chronically ill patient. She was affected by recurrent respiratory infections, since pediatric age (3 years),

Gene sequencing for the constant region of Kappa chain showed a T to G substitution at the position 1288 (rs200765148; ClinVar ID: