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**Reference Values for Immunoglobulin Kappa and Lambda Light Chains and the Kappa/Lambda Ratio in Children’s Serum**

**Maddalena Saitta,1 Alberto Iavarone,1 Nasario Cappello,2 Maria Rose Bergami,3 Giovanni Carlo Fiorucci,1 and Francesco Aguzzi1,4**

We analyzed 708 serum samples from healthy children and adolescents by immunonephelometry to obtain reference values for the immunoglobulin kappa (κ) and lambda (λ) light chains and for their ratio at a time of life when immunoglobulin synthesis is maturing and continually being stimulated. The λ chain concentration that is to be maintained throughout the child’s life is reached very early, just after 1 year, whereas the concentration of the κ chains, which increases gradually, reflects the concentration of the immunoglobulins as a whole. These reference values may be useful for studying κ and λ chains in illnesses involving the immune system in children.

Additional Keyphrases: pediatric chemistry · immune status · immunonephelometry · age-related effects

Since reliable, completely automated commercial methods for quantifying immunoglobulin kappa (κ) and lambda (λ) light chains in serum became available to the clinical laboratory (1), the implications of their ratio (κ/λ) have been widely studied in adults. Most reports stress the imbalance between the two chains induced by the presence of a monoclonal component in monoclonal gammopathies (2–4). The new index, the ratio, seems to be more useful in monitoring than in screening monoclonal components with high sensitivity and specificity (5–8).

The κ/λ ratio has been less studied in children. In 1986 Renckens et al. (9) measured the concentrations of κ and λ light chains in serum of normal and diseased children by immunonephelometry. They noted that although the κ chain concentration gradually increases with age, the λ chain concentration remains more or less constant in both diseased and control children.
Humoral immunity develops continuously throughout childhood. Some pathologies usually seen in adults are now being seen in children, such as findings of monoclonal components in cancer (10) or after organ or bone marrow transplantation (11–13). Babies and children with congenital infection with human immunodeficiency virus show the same abnormal immunoglobulin synthesis as do affected adults (14–16). For these reasons and others, we were interested in determining these new immunological indexes and their reference values for children.

**Materials and Methods**

**Subjects**

We evaluated 708 subjects, 399 boys and 309 girls, attending the outpatient department of Regina Margherita Children's Hospital in Turin for blood tests between May 1989 and June 1991. Of the subjects, 664 were children, ages 1 month to 13 years; and 44 were adolescents, ages 14–20 years. All subjects were apparently healthy and well nourished. From clinical data and interviews with the subjects' accompanying relatives, who gave informed consent for the collection of blood samples, we concluded that the subjects were free from acute infections or chronic disorders involving the immunological system. The children had generally been sent to the laboratory to be tested for asthenia or pallor on parental insistence or for screening before surgery (removal of tonsils, urethrocele, strabismus, etc.).

All subjects displayed a normal gamma zone on serum electrophoresis. IgG, IgA, and IgM were within the normal range (17). Tests for C-reactive protein were negative.

**Immunonephelometry**

We quantified κ and λ light chains nephelometrically with the Beckman instruments (Galway, Eire) APS immunonephelometric system, using a Beckman calibrator (Cal I, lot M912127) and antisera. The serum samples, obtained by centrifugation, were examined at once or frozen at −20 °C until being tested. A control serum sample (Beckman Control 1, lot M980116) was inserted at the beginning and end of every series; the resulting total of 70 control assays over 18 months yielded interseries CVs of 4.7% and 4.3% for κ and λ, respectively.

**Statistical Analysis**

The data were divided into 14 age groups for analysis: two groups for the first year of life (0–6 months; 6–12 months), one group per year up to year 9, and one group each for ages 10–11, 12–13, and 14–20 years. We compared the averages for κ and λ chains for contiguous age groups and within each age group by two-way analysis of variance with confidence limits corrected by the Bonferroni (18) method. The Student–Newman–Keuls (19) multiple-range test was used to suggest the possible merging of age groups, which enabled us to tabulate reference values by age. Statistical evaluations were performed with the BMPD programs (20).

**Results**

Results of the analysis of variance show that changes in the concentrations of the κ and λ light chains in the population examined are significantly different and that values for each chain are considerably influenced by age (Figure 1). The Bonferroni test showed a highly significant difference between values for the two chains (P <0.001) from the end of the first year of life on. Thereafter, the curves for the two light chains showed a progressive discrepancy. The κ chain concentration greatly increased between years 1 and 2 (P <0.001). The change was then progressive, becoming marked between ages 4 and 5 years (P <0.05), until stable values were reached from year 7 onwards.

By contrast, λ chains, after a significant increase between years 1 and 2 (P <0.05), remained almost constant throughout childhood and adolescence.

Reference values calculated by parametric and nonparametric methods are shown in Table 1. To account for the asymmetrical distribution of the population in the groups, we chose the interval between the 5th and 95th percentiles as our reference range.

For the κ chain, values from consecutive age groups

![K and L chain trend](attachment://k_and_l_chain_trend.png)

**Table 1. Reference Values for κ and λ Chains at Different Ages**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>No. of cases</th>
<th>Mean (2SDs)</th>
<th>Mean ± 2 SD range</th>
<th>5th–95th percentile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>66</td>
<td>4010 (2620)</td>
<td>1390–6630</td>
<td>1770–6870</td>
</tr>
<tr>
<td>1–3</td>
<td>104</td>
<td>6140 (2640)</td>
<td>3500–8780</td>
<td>3560–8390</td>
</tr>
<tr>
<td>3–5</td>
<td>131</td>
<td>7060 (2940)</td>
<td>4120–10000</td>
<td>4950–10000</td>
</tr>
<tr>
<td>5–7</td>
<td>122</td>
<td>8250 (2680)</td>
<td>5390–11 110</td>
<td>5570–10 200</td>
</tr>
<tr>
<td>7–20</td>
<td>285</td>
<td>9090 (3720)</td>
<td>5370–12 810</td>
<td>6240–12 300</td>
</tr>
</tbody>
</table>

**Kappa chain**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>No. of cases</th>
<th>Mean (2SDs)</th>
<th>Mean ± 2 SD range</th>
<th>5th–95th percentile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>66</td>
<td>3280 (2800)</td>
<td>480–6080</td>
<td>1690–5730</td>
</tr>
</tbody>
</table>

**Lambda chain**

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Table 2. Reference Values for ω/λ at Different Ages

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of cases</th>
<th>Mean (2SDs)</th>
<th>Mean ± 2 SD range</th>
<th>5th-95th percentile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>66</td>
<td>1.27 (0.62)</td>
<td>0.65–1.89</td>
<td>0.788–1.87</td>
</tr>
<tr>
<td>1-3</td>
<td>104</td>
<td>1.43 (0.58)</td>
<td>0.85–2.01</td>
<td>0.969–1.89</td>
</tr>
<tr>
<td>3-6</td>
<td>204</td>
<td>1.69 (0.62)</td>
<td>1.07–2.31</td>
<td>1.22–2.51</td>
</tr>
<tr>
<td>6-20</td>
<td>334</td>
<td>2.01 (0.84)</td>
<td>1.17–2.85</td>
<td>1.42–2.80</td>
</tr>
</tbody>
</table>

Discussion

ω/λ ratios in children still have not been thoroughly investigated even though the synthesis of immunoglobulins increases progressively during childhood because of the physiological maturation of the B-immune compartment and its active stimulation by antigens. Moreover, pathological conditions in children often involve quantitative alterations of immunoglobulin concentrations, whether as hypo- or hypergammaglobulinemia. We determined reference values for ω and λ chains and their ratio in serum samples of children attending our outpatient department, following the rules recommended for reference values in populations of children (21).

The trend we observed for ω and λ chains overlaps with that found by Rencens et al. (9) in a smaller number of cases. After the first year of life, when the maternally derived antibodies have been catabolized and children have become fully capable of synthesizing their own immunoglobulins, we find an increase in the concentrations of both chains but a particularly significant increase in the λ chains. Apparently, the maturity of the ability to synthesize λ-type immunoglobulins is very rapidly achieved, whereas the ability to synthesize κ-type immunoglobulins develops more slowly.

The stability of the λ chain concentration until a very advanced age was also reported by Singh and Kulig (22), who found that the κ chains continue to increase, even in subjects older than 79 years. ω/λ increases gradually with age, paralleling the increase in κ chains.

In monoclonal gammapathies in adults, major clinical information is obtained from the ω/λ ratio, but its usefulness in children’s pathology is limited. Nevertheless, it would be of interest to study the behavior of ω and λ chains in the immunological disorders of childhood. In our experience, for example, children of different ages with symptomatic infection with human immunodeficiency virus nearly always have low ω/λ values (data not shown), as if the hyperactivation of the B-cell compartment generally seen in these subjects was directed more toward the synthesis of λ immunoglobulins.

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References


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For sera with iron (Fe) concentrations <4 μmol/L, Kodak Ektachem slides Generation (GEN) 14 (without ascorbic acid) yielded systematically lower results for Fe than did liquid Ferrozine-based reagents from Baker containing ascorbic acid (10 g/L, final concentration) and adapted to Cobas-Bio. During an 8-month comparison period, outliers (defined as [Fe]_{cobas} - [Fe]_{kodak} >4 μmol/L) were seen in 21 of the 8731 sera (0.24%) tested, corresponding to <5% of the sera with [Fe]_{kodak} <4 μmol/L. In vitro addition of ascorbic acid and (or) Fe identified at least two types of outliers: type 1 (~70%), characterized by [Fe]_{kodak} >0.4 μmol/L, by (supra)normal Fe recovery in Kodak slides in the presence or absence of ascorbic acid (10 g/L), and by between-method differences in serum Fe (Cobas - Kodak) that were significantly correlated with serum Zn content (P <0.0004); and type 2 (~30%), tentatively ascribed to contamination by EDTA, with serum Fe by Kodak <0.4 μmol/L and Fe recovery near 0%, both of which could be significantly and dose-dependently increased by addition of ascorbic acid (5-20 g/L). For both types of outliers, flameless atomic absorption spectrometry (AAS) yielded results that were significantly higher than concentrations by Kodak with GEN 14. Use of GEN 16 slides (containing ascorbic acid) improved concordance of Kodak results with Cobas, and hence with flameless AAS, for both types of outliers; abolished Zn dependency of results; and increased Fe results in sera with type 2 outliers, although these remained substantially lower than by Cobas. However, like other ascorbic acid-containing reagents, GEN 16 slides were more sensitive to interference by dextran-bound Fe, as assessed during in vitro addition experiments and comparisons involving samples from Fe-dextran-treated patients. GEN 16 slides are hence expected to more frequently overestimate the physiologically available protein-bound Fe in hemodialysis patients. In hospital laboratories, this new interference will probably arise more frequently than the spuriously low results with GEN 14, hence warranting further efforts in optimizing Fe slides.

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**Additional Keyphrases:** oxidants · chelators · EDTA · citrate · zinc · divalent ions · multilayer film analysis · spectrophotometry · atomic absorption spectrometry

We previously showed (1) that Kodak Ektachem slides [Generation (GEN) 14; Eastman Kodak, Rochester, NY] for determining iron (Fe) and total Fe-binding capacity in serum yielded results that correlated very significantly with data obtained with ascorbic acid-containing liquid Ferrozine reagents (J.T. Baker, Deventer, The Netherlands) adapted to a Cobas-Bio centrifugal analyzer (Roche Diagnostics, Basel, Switzerland) and with flame atomic absorption spectrometry (AAS; Instrumentation Laboratory, Wilmington, MA). Moreover, Kodak slides proved superior to both other technologies in that the multilayer film elements more exclusively measured the (patho)physiologically rele