Pathology (August 2015) 47(5), pp. 452–461

CHEMICAL PATHOLOGY

Trends and physiology of common serum biochemistries in children aged 0–18 years

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Summary

The aim of this study was to visually present and discuss in detail the physiological trends of 22 serum biochemistries in children aged 0–18. A data-mining, LMS (lambda, mu, and sigma) approach was employed to derive the smoothed continuous serum biochemistry centile charts, after application of stringent outlier exclusion criteria. Serum sodium and calculated osmolality are low in early life and rise with age due to maturing kidney and body water redistribution. Urea, creatinine and uric acid is high at birth, declines to reach a trough by 1 month of age and gradually rises again thereafter. Serum bicarbonate falls initially during the neonatal and toddler period, then rises with declining respiratory rate, further increasing sodium and suppressing chloride. Potassium, calcium and phosphate are required for somatic growth and are actively accrued during periods of rapid growth. Albumin increases until puberty while globulin rises to age 10 as a result of increased hepatic synthetic capacity and maturing immunity. Serum alkaline phosphatase activity peaks during bone growth spurts in infancy and adolescence due to osteoblast leakage, while creatinine increases with muscle mass. Serum gamma-glutamyl transferase, aspartate aminotransferase and lactate dehydrogenase activities are high at birth and decline with age. Serum alanine aminotransferase activity is low at birth and is induced by increased gluconeogenesis. Serum bilirubin increases continuously with age, mirroring haemoglobin concentration. Serum total cholesterol declines more markedly in boys than girls during puberty due to the combined effects of free testosterone (lowering high-density lipoprotein cholesterol in boys) and oestradiol (lowering low-density lipoprotein cholesterol in boys and girls). It is important to understand trends and biological variation when interpreting results since partitioned reference intervals may mask this information.

Key words: Biochemistry, centile chart, children, development, growth, paediatrics, physiology, reference interval, trends.

Received 11 October 2014, revised 18 March, accepted 24 March 2015

INTRODUCTION

The paediatric population is marked by continuous growth and development that brings about changes in various aspects of their physiology, including serum biochemistry.[1–4] For example, it is well recognised that serum alkaline phosphatase activity increases as a child reaches puberty, reflecting rapid bone growth, and declines towards adulthood.

Within-person biological variation is the amount of fluctuation around the set point of a biological parameter in an individual.[3–5] By contrast, between-person biological variation is the difference in set point between individuals. Reference intervals reflect the combined biological variation in a reference population. The index of individuality is the ratio of within-subject biological variation to the between-subject variation. Knowledge of such physiological changes is important for the understanding and interpretation of paediatric serum biochemistry in clinical practice.

An analyte with a high index of individuality (>1.4) indicates that the reference interval would be helpful in classifying the homeostatic state of the subject. By contrast, a low index of individuality (<0.6) indicates the reference interval would have limited use. The impact of index of individuality is most apparent when repeat testing is undertaken to assess a patient.[5] Yet, these physiological trends and data in children are not well described in the literature owing to the significant ethical, operational and logistical challenges associated with obtaining blood samples from this population.[2]

We recently described the application of a statistical approach to obtain smoothed centile charts and within-person and between-person biological variation data of several common serum biochemistries in a large paediatric population.[2–4] Here, the physiology underlying the biological trends of 22 serum biochemistries from those studies are discussed in detail to improve the understanding of their physiological changes and clinical implication in growing children.

MATERIALS AND METHODS

This study did not require institutional review board approval where it was carried out. The details of the statistical approaches used to derive the biochemistry centile charts have been described previously.[2]

Briefly, the de-identified biochemistry results of a large population of children aged between 0 and 19 years ($n = 56{,}712$), who visited their primary care physician, were extracted from the laboratory information system of a large laboratory network in Queensland, Australia. The biochemistry tests were performed over the period of 1 year, ending on 30 September 2013. Biochemistry results obtained from samples with haemolysis or icteric indices above the thresholds recommended by the manufacturer,[2] which may interfere with the laboratory analysis, were removed. Outlier biochemistry results were identified and excluded according to Tukey's criteria.[6] To obtain the biochemistry centile charts, children who had biochemistry tests performed only once during the study period were included. The anion gap was calculated by [sodium – chloride – bicarbonate (all in mmol/L)]. The globulin concentration was calculated by [total protein – albumin (both in g/L)], while the osmolality was calculated by [1.86 × sodium + glucose + urea + 9 (all in mmol/L)].

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: 10.1097/PAT.0000000000000274

The biochemistry results of children with a single testing episode were used to construct smoothed centile charts using maximum penalised likelihood estimation technique to determine the Box-Cox transformation λ (L), median μ (M), and coefficient of variation σ (S) as cubic smoothing splines by non-linear regression (LMS ChartMaker Light software, version 2.54; Medical Research Council, UK).[7–9]

Separate charts were constructed for selected analytes to better display the dynamic changes during the first year of life. For these analytes, the outlier detection was performed using a combination of Tukey's criteria and visual inspection of the scatter plot.

RESULTS

The smoothed centile charts for the biochemistry results are shown in Fig. 1 and 2. In all, 546 children who were less than 1 year of age (of whom 38% were less than 0.2 years; 39.2% were girls) were included in this study. The trends of the biochemistry should be interpreted from the median lines (50th centile, solid line) of the charts, since it is the most stable and representative of physiology. Care should be exercised when studying the charts as the scale on the y-axis can exaggerate magnitude of change.

Serum urea and creatinine were high at birth and declined rapidly within the first few weeks of life before increasing gradually thereafter. By contrast, calculated anion gap rose during infancy before declining after the first year. Sodium and calculated osmolality showed an upward trend while chloride showed a downward trend with increasing age. Of note, the

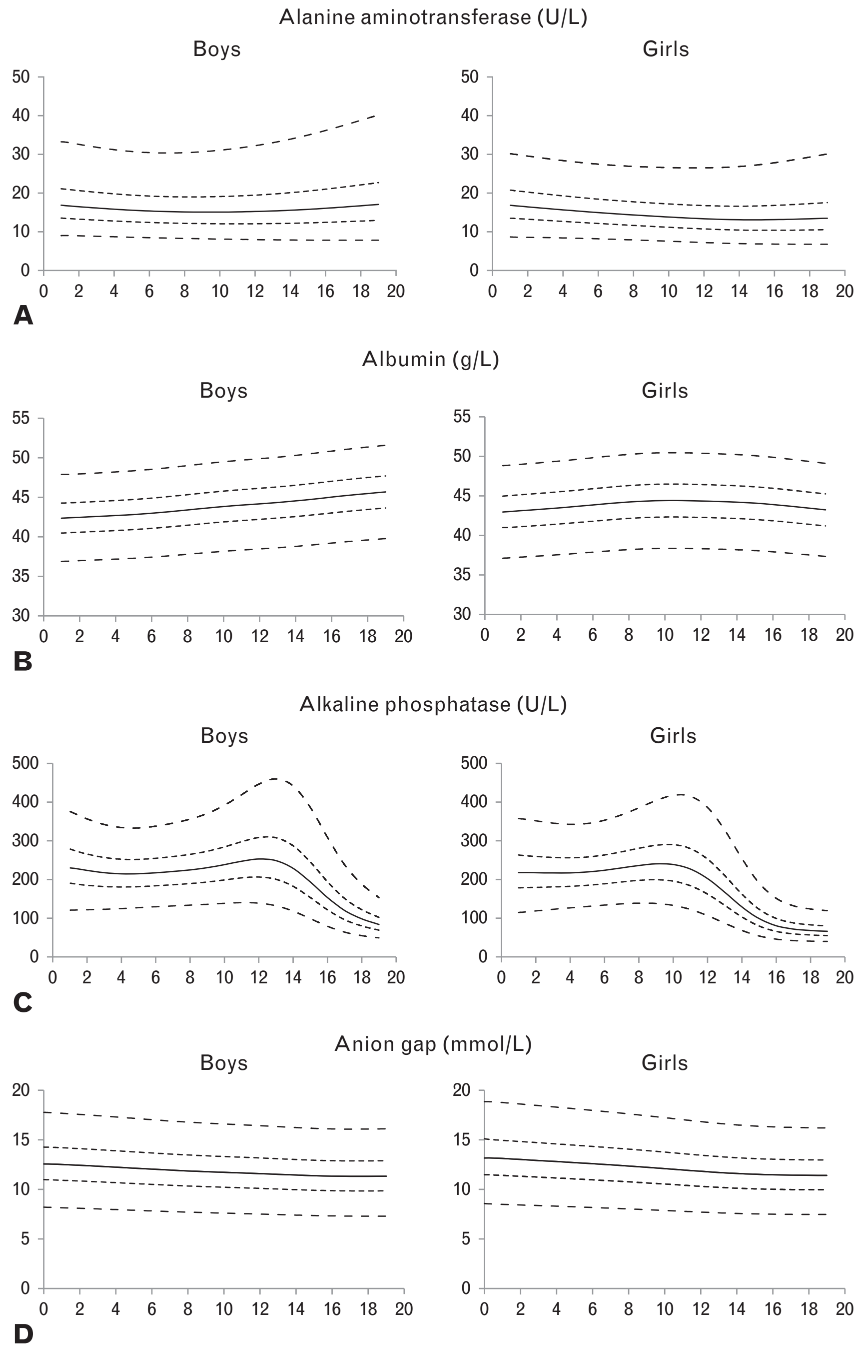

Fig. 1 The trends of serum biochemistry for boys (left) and girls (right). On the y-axis: the solid line represents the 50th percentile; the lower and upper dotted line represents the 25th and 75th percentiles; the lower and upper dashed lines represent the 2.5th and 97.5th percentiles. On the x-axis: the age is expressed in years. *Please see Fig. 2 for expanded view of the trends for children less than 1 year of age.