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Short communication
Kratko saopštenje

POPULATION-BASED PEDIATRIC REFERENCE INTERVALS IN GENERAL CLINICAL CHEMISTRY: A SWEDISH SURVEY

PEDIJATRIJSKI REFERENTNI INTERVALI U OPŠTOJ KLINIČKOJ HEMIJI ZASNOVANI NA ISPITIVANJU POPULACIJE: ŠVEDSKO ISPITIVANJE

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Summary: Very few high quality studies on pediatric reference intervals for general clinical chemistry and hematology analytes have been performed. Three recent prospective community-based projects utilising blood samples from healthy children in Sweden, Denmark and Canada have substantially improved the situation. The Swedish survey included 701 healthy children. Reference intervals for general clinical chemistry and hematology were defined.

Keywords: biomarker, children, clinical chemistry tests, pediatric, reference interval, reference range

Kratak sadržaj: Postoji vrlo malo visokokvalitetnih studija o pedijatrijskim referentnim intervalima za opšte analite u kliničkoj hemiji i hematologiji. Nedavno su tri prospektivna projekta zasnovana na ispitivanjima u okviru zajednice uzoraka krvi zdrave dece u Švedskoj, Danskoj i Kanadi znatno popravila situaciju. Švedsko ispitivanje obuhvatilo je 701 zdravo dete. Definisani su referentni intervali za opštu kliničku hemiju i hematologiju.

Ključne reči: biomarker, deca, testovi u kliničkoj hemiji, pedijatrijski, referentni interval, referentni opseg

Introduction

The clinical chemistry reference interval is one of the most important decision making tools used to distinguish between healthy and diseased individuals. Reference intervals should be established by measurements on blood samples from healthy subjects who are defined with respect to age and sex, and preferentially also ethnic group. In the NORIP project clinical chemistry analytes were measured in samples from 3600 healthy adults from the five Nordic countries. These reference intervals were implemented in most Nordic laboratories ten years ago. However, similar prospective population-based reference interval studies in healthy children are rare. One of the main reasons is the ethical issues around taking blood samples from healthy children. Also, pediatric reference interval studies require many participants as they should reflect the different phases of physiological development from birth to adolescence. However, major advancements have recently been achieved with the publication of data from the CALIPER initiative in Canada, as well as projects from Sweden and Denmark.

Methods

In the population-based Swedish study venous blood samples were obtained from 701 healthy children aged 6 months to 19 years. The children were primarily of Swedish origin; ethnic background was not recorded. The children were recruited in child-care centers, kindergartens and schools in the Falun

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Non-standard abbreviations: NORIP, Nordic Reference Interval Project; CALIPER, Canadian Laboratory Initiative on Pediatric Reference Intervals; EDTA, ethylenediaminetetraacetic acid.

area in central Sweden. Patients with chronic disease or infection in the last 10 days were asked not to participate. A questionnaire which included questions about health, diseases, allergies and medications was completed.

The children were not fasting. Blood sampling included serum and EDTA tubes. Age and gender specific pediatric reference intervals were defined for approximately 50 general clinical chemistry, hematology and certain endocrine components. Instruments used were Abbott Architect (general chemistry), Siemens Bayer Advia (hematology) and Mono S and Tosoh systems (HbA1c). To facilitate the use on other platforms, NORIP's serum X was used for traceability to recognized reference materials.

The statistical treatment was similar to the principles used in the NORIP project. This includes calculation of nonparametric 2.5^{th} and 97.5^{th} percentiles, Dixon's test for detecting outliers, and partitioning due to age and gender differences according to the Lahti model used in NORIP. Partitioning with respect to age was performed as »educated guesses« on the basis of previously published data, and a graphic visualization of the data for individual analytes.

Results and Discussion

Details of the results in the Swedish study for general clinical chemistry, hematology and certain hormones are available (1–4). The Swedish study only contains data on children older than 6 months of age. This creates a practical problem when implementing the data in the clinical routine. Most analytes show large changes in healthy children during the first weeks or months after birth. One practical solution may be to add comments to the laboratory reports with a warning that reference intervals are lacking for the youngest age group. The drawback is that in today's laboratory information systems and electronic health records such a procedure will not generate any alerts for pathological results. Alternatively, pragmatic extra-polations for the youngest children based on liter- ature references, such as the Canadian CALIPER project, could be used for extrapolation where gaps still exist.

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