AAT deficiency in the propositus, although the phenotypic IEF analysis was in agreement with her diminished pulmonary function. Genotyping for S and Z alleles has become a routine laboratory test. However, it is important to realize that these tests might give misleading results, as shown in this case. One should always be aware of the possible presence of alleles such as M_{Heerlen} if a standard genotypic analysis is not in agreement with serum AAT values and/or IEF analysis. Recognition and awareness of these caveats warrant reliable molecular genotyping test results. If an allelic variation such as M_{Heerlen} is suspected in an individual, it is important to realize that there are many possible variants that may also account for discrepancies such as those reported here (7).

To detect any of these variants one could use an aselective prescreening method to detect the presence of mutations per se. A variety of methods to detect single nucleotide polymorphisms and small deletions or insertions are currently available, e.g., single strand conformation polymorphism analysis, heteroduplex analysis, and enzymatic mutation detection. If an aberration is found, the exact mutation can be identified by sequence analysis. The alternative would be to sequence entire genes or coding regions. However, AAT gene mutations are all named after the town of Heerlen.

To our knowledge, the combination of a Z and a M_{Heerlen} allele has not been described before now. As can be expected from the AAT concentration, the pulmonary function in the two sisters is affected to a degree similar to that seen in Pi ZZ individuals. One can only speculate about potential liver involvement at a young age because deposition of AAT in hepatocytes does not seem to complicate M_{Heerlen} homozygosity. The risk of juvenile cirrhosis in Pi ZZ individuals, as a result of deposition of AAT in inclusion bodies, is well known. Compound heterozygotes for Z and M_{Heerlen} might have an intermediate risk for liver involvement.

References

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Lactic Acid Dimer: An Artifact in the Gas Chromatographic Analysis of Urine with Massive Lactic Acid Aciduria

To the Editor:
In severe lactic acidosis (1–4), secondary increases of pyruvic acid, 2-hydroxybutyric acid, and 4-hydroxyphenylactic acid are common (5). We describe such a case in which we also found lactic acid dimer.

A premature baby, born at 31 weeks of gestation, had hyperbilirubinemia, sepsis, anemia, thrombocytopenia, dermatitis, and metabolic acidosis. Gas chromatography–mass spectrometry (GC-MS) of urine (6) from the infant revealed the following concentrations: lactic acid, 83 100 mmol/mol of creatinine (reference interval, 0–25 mmol/mol of creatinine); 4-hydroxyphenylactic acid, 3755 mmol/mol of creatinine (reference interval, 6–28 mmol/mol of creatinine); pyruvic acid, 3679 mmol/mol of creatinine (reference interval, 0–12 mmol/mol of creatinine); 2-hydroxyisovaleric acid, 506 mmol/mol of creatinine (reference interval, 0–3 mmol/mol of creatinine); and lactic acid dimer, 707 mmol/mol of creatinine (absent in urine from healthy individuals). The spectrum of the trimethylsilyl derivative of lactic acid dimer (lactyl lactate) matched that in Ref. (7).

Ketting et al. (7), who described the occurrence of lactic lactate in the urine of patients with inherited metabolic diseases, including those with inherited lactic acidosis, ascribed its occurrence to the biochemical activity of intestinal bacteria. We attempted to find the origin of the lactic acid dimer. The organic acids in a urine sample from a healthy subject were analyzed, and no lactic acid dimer was found in that specimen. To another specimen from the same subject, we added the same concentration of lactic acid per mole of creatinine as was measured in our patient. By GC-MS, lactic acid and lactic acid dimer were found at concentrations of 83 000 and 700 mmol/mol of creatinine, respectively, values similar to those found in the patient’s specimen. Thus, the presence of lactic acid dimer appeared to be an artifact in the GC-MS analysis of urine with massive lactic acid aciduria.

Resins of chromatographic media are well known to catalyze organic reactions of various natures (8). Work is under way in this laboratory to determine whether the addition of...
high concentrations of major metabolites to urine in certain metabolic disorders, such as propionic acidemia and methylmalonic acidemia (9), lead to the production of an abnormal metabolite(s) at the high temperatures used for GC-MS analysis.

References

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Correction
In the article by W.L. Roberts, L. Moulton, T.C. Law, G. Farrow, M. Cooper-Anderson, J. Savory, and N. Rifai, entitled “Evaluation of Nine Automated High-Sensitivity C-Reactive Protein Methods: Implications for Clinical and Epidemiological Applications. Part 2” (Clin Chem 2001;47:418–25), in Table 1, the limits of detection for the Kamiya and Roche methods should read 0.03 and 0.02 mg/L, respectively, not 0.32 and 0.21. The authors apologize for this error.