Hereditary fructose intolerance and $\alpha_1$ antitrypsin deficiency

G Hillebrand, R Schneppenheim, H D Oldigs, R Santer

Abstract

A patient with coexisting hereditary fructose intolerance (HFI) and $\alpha_1$ antitrypsin deficiency ($\alpha_1$ATD) is described. Protease inhibitor typing was not conclusive, presumably because of impaired N-glycosylation secondary to HFI. The case underlines the diagnostic role of molecular genetic techniques in inborn errors of metabolism.

(Keywords: $\alpha_1$ antitrypsin deficiency; hereditary fructose intolerance; molecular genetics; protease inhibitor typing)

Both $\alpha_1$ antitrypsin deficiency ($\alpha_1$ATD) and hereditary fructose intolerance (HFI) are important differential diagnoses in infants with cholestatic liver disease and failure to thrive. Because of their extremely rare occurrence, the potential problems in diagnosis resulting from an overlap of clinical symptoms, and the fact that the conventional diagnostic variable of one disease, electrophoretic mobility of the protease inhibitor (PI), is affected by the presence of a second disorder, we describe a patient in whom coexistence of $\alpha_1$ATD and HFI was ultimately confirmed by molecular genetic methods.

Case report

A term male neonate (2840 g, 49 cm) presented at age 4 weeks with vomiting, pale loose stools, and failure to thrive (3150 g) while being fed an infant formula (PreHumana, Herford, Germany) containing lactose. As stool consistency and vomiting worsened, a term male neonate (2840 g, 49 cm) was changed to a medium chain triglyceride-containing formula (Portagen; Mead Johnson, Darmstadt, Germany; 2.0 g sucrose/100 ml). While small amounts of vegetable were introduced into the diet at age 3 months, vomiting exacerbates and the patient was referred to us. Recently, at the patient’s age of 14 years, we were able to confirm both diagnoses using molecular genetic methods (fig 1): the patient was found to be homozygous for both the common Ala150Pro mutation of HFI and the Glu342Lys mutation of $\alpha_1$ATD(ZZ). His asymptomatic brother was homozygous for $\alpha_1$ATD(ZZ) both by isoelectric focusing and molecular genetic testing.

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About 4% of the northern European population are carriers of, and consequently about 1 in 2500 is homozygous for, \( \alpha_1 \)-antitrypsin deficiency. For HFI, it has been estimated that up to 1 person in 20,000 is born with this metabolic disorder. Thus, on the basis of the known location of the genes involved on two different chromosomes, coexistence of the two diseases in a patient has to be expected in about 1 in 40 million. With this rare occurrence, a false positive diagnosis of one of the two diseases had to be considered in this case. An incorrect diagnosis of HFI seemed unlikely, as determination of enzyme activity in the liver was based on ratios, as usually performed with fructose 1,6-bisphosphate as substrate, which should eliminate decreased activities secondary to parenchymal injury. Furthermore, enzyme activity in small intestine, a tissue not affected by \( \alpha_1 \)-ATD, was investigated, and this confirmed the diagnosis of HFI. However, hypoglycosylation of proteins is known in patients with HFI. Hypoglycosylation is normally identified by a mobility shift of serum sialotransferrins on isoelectric focusing, but it also affects other glycoproteins. In retrospect, we interpret the potentially misleading result of PI typing as a consequence of coexisting HFI. It has only recently been reported that fructose 1-phosphate, which accumulates in HFI, is an inhibitor of phosphomannose isomerase, the first enzyme of the N-glycosylation pathway, thus explaining N-glycosylation disturbances in HFI. In our case, coexistence of HFI and \( \alpha_1 \)-ATD was finally confirmed by molecular genetic techniques. Thus molecular genetic diagnosis offers the advantage of not being influenced by secondary effects of coexisting diseases, and also circumvents invasive approaches—for example, liver biopsy—often necessary for conventional diagnostic methods.

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