A Case of Partial Deficiency of $\alpha_1$-Antichymotrypsin

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A 20-year-old woman, admitted to a neurological ward with a diagnosis of benign intracranial hypertension, was found on specific protein electroimmunoassay to have a consistently decreased concentration of $\alpha_1$-antichymotrypsin in her plasma. Serum from her father showed the same result. Further investigation of her family demonstrated that this partial deficiency was transmitted in an autosomal dominant fashion and was not associated with any obvious specific clinical abnormalities.

Additional Keyphrases: reference interval · genetics · autosomal dominant transmission · heritable disorders

Human $\alpha_1$-antichymotrypsin ($\alpha_1$X) is an inhibitor of certain proteases. Kinetic data, measuring the half-time of association between inhibitor and selected proteases, suggest that $\alpha_1$X is a physiological inhibitor of the chymotrypsin-like proteases cathepsin G (EC 3.4.21.20), which is secreted by neutrophils, and chymase (EC 3.4.21.39), secreted by mast cells (1). Concentrations of this protein, a major acute-phase reactant, rapidly increase in plasma after an inflammatory stimulus. No deficiency states of this inhibitor have previously been described and thus their clinical significance is unknown.

As part of a routine plasma protein screen, we measure $\alpha_1$X as an indicator of inflammation. Recently we discovered decreased concentrations of this inhibitor in a patient. Investigations of her family demonstrated that the deficiency is familial.

Materials and Methods

The following specific proteins were measured in serum: albumin, prealbumin (transthyretin), transferrin, $\alpha_1$-antitrypsin, orosomucoid, haptoglobin, ceruloplasmin, C-reactive protein, $\alpha_2$-macroglobulin, IgG, IgA, and IgM. Albumin was measured by continuous flow (SMAC; Technicon method no. SG4-0030FD). The other specific proteins were measured by electroimmunoassay (2, 3) with use of specific antisera from Dakopatts, Denmark. A.I.P. Reference Serum from Technicon Chemicals, Belgium, was used as a standard, except for prealbumin and $\alpha_1$X, for which we used standard human serum and protein standard plasma, respectively, both from Behring Diagnostics, F.R.G. The $\alpha_1$X concentrations are reported as a percentage of the mean value (0.48 g/L) for a 1000-donor normal pool. The normal reference interval is 70%–130% (0.34–0.62 g/L). For $\alpha_1$-antitrypsin phenotyping we used isoelectric focusing on thin-layer polyacrylamide gel (4).

Case Report

The patient, a 20-year-old woman, was admitted for investigation of bilateral papilloedema. On admission she gave a one-week history of retro-orbital and bifrontal headache. Computerized axial tomography excluded any space-occupying lesion and she was diagnosed as having benign intracranial hypertension with cerebrospinal fluid pressure of 42 cm of mercury (156 kPa). Values for electrolytes and for liver- and renal-function tests were within normal limits, as they were for a complete blood-cell count.

Results of specific-protein assays, done as part of an electrophoresis screen, were normal except for $\alpha_1$X, which was 0.24 g/L, half the mean normal concentration. Measured on four further occasions, this value consistently fell between 45 and 55% of normal.

The patient was treated with diuretics (acetazolamide and cyclopentiazide) and was discharged from the hospital six weeks later.

Before this illness she had had an uneventful medical history. Because the $\alpha_1$X concentration, although consistently low, was unlikely to be related to her neurological condition, we examined her family to determine whether the deficiency was familial. The results are summarized in Figure 1. Her brother, sister, and mother had normal values for $\alpha_1$X, but her 42-year-old father and 83-year-old grandmother had a subnormal $\alpha_1$X concentration. Her father is a sickness beneficiary as a result of a major road accident, prior to which he had been in good health apart from the usual illnesses of childhood. Her grandmother was in good health and had an unremarkable health history.

All of the other affected individuals appear to be well, and there were no apparent medical problems connected with the deficiency. Some also had heterozygous $\alpha_1$-antitrypsin deficiency, which was not linked to the $\alpha_1$X deficiency. Concentrations of the other proteins measured were all within normal limits in all cases.

Discussion

The familial pattern of the $\alpha_1$X deficiency in this family makes a genetic defect probable. The transmission is apparently autosomal dominant and the affected members are heterozygotes. The partial deficiency state does not appear to have any clinical significance. This observation is similar
to heterozygous $\alpha_1$-antitrypsin deficiency, in which $\alpha_1$-antitrypsin concentrations are 60% of normal and which also has no clinical significance unless the lungs are stressed by smoking or other similar insult.

Although we have not found a clinical syndrome associated with this partial deficiency, the physiological importance of $\alpha_1$X in inflammation is suggested by the rapid increase in its concentration in plasma in acute inflammation. This increase occurs within 8 h, about twice as fast as that for $\alpha_1$-antitrypsin, and its relative increase is twice as great. The physiological function of $\alpha_1$X appears to be inhibition of cathepsin G (1). Although the physiological role of cathepsin G has not been established, it can act as an angiotensin-converting enzyme (5) and neutrophil degranulation may result in local production of angiotensin II at sites of inflammation. Increased $\alpha_1$X may be important in restricting this type of activity to sites of inflammation. Because the physiological significance of this inhibitor protease system is still unknown, possible clinical manifestations of a deficiency state cannot be predicted. This case, demonstrating heterozygous (partial) deficiency of $\alpha_1$X, suggests that a homozygous deficiency is possible. Although this has not been described, it may clarify the physiological role of $\alpha_1$X if it is associated with a clinical syndrome.

Note added in proof: Since this paper was accepted, we have found a similar deficiency in two other unrelated families.

References
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