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Classification of Antithrombin III Deficiencies – Has a New Tower of Babel Been Built?

Dear Sir,

In a recent issue of your journal Hultin et al. (1) discussed antithrombin Oslo and reviewed 33 other variants of congenital antithrombin III (AT-III) deficiencies. This paper demonstrates the difficulties of classifying congenital AT-III deficiencies, since now it has turned out, that the "most classical" AT-III deficiency described by Egeberg in 1965, ironically, is not "classical" at all, as it has been defined. Their paper clearly shows the inadequacy of the classification systems currently used (including our own). The authors discussed the AT-III deficiencies creating some confusion, owing mainly to the lack of a generally accepted classification system. For example, in the introduction of their paper they state: "All of the Type III variants (and none of Type II) demonstrated an abnormal peak, more cathodal than the normal AT antigen peak, by crossed immunoelectrophoresis (CIE) with heparin in the first dimension". However, in Table 2, they indicated 4 Type II variants with abnormal cathodal peaks. They designated our Type 1/b variant described in 1980 (2) as AT-III Budapest 2, while we ourselves called AT-III Budapest 2 another variant, characterized by normal AT-III antigen concentration and the isolated disturbance of the heparin-AT-III reaction (3). Other publications, too, reflect the chaos in the nomenclature: some variants have been designated with toponyms while others not. Even, an apparently normal isoform of AT-III was marked with toponym.

Before discussing the classification systems presently used, one may ask whether we need them at all? By the exact biochemical characterization of the particular variants we can define them precisely, rendering unnecessary any arteficial classifications and forcing them into the Prokusthes' bed of the human mind. However, despite the attractiveness of this opinion, we need a classification system, mainly for clinical purposes. First, in the majority of the cases the exact molecular defect has not been clarified. Second, some variants are clinically quite different, requiring different diagnostic and therapeutic approach. Third, we cannot expect a "perfect" classification system in the near future: application of the molecular genetic techniques in the survey of AT-III deficiencies suggests that AT-III deficiencies are more heterogeneous and complex than it has ever been supposed (4).

Historically, the necessity of classification of AT-III deficiencies arose, when we described the first abnormal AT-III variant in 1974 (5). At that time and for the coming 5 years Type I ("classical") AT-III deficiencies designated the cases characterized by quantitative deficiency of AT-III (measured by functional and immunological methods), while Type II deficiencies included the cases with normal antigen concentration but low functional activity. In 1979, Nagy et al. (6) found a new AT-III variant displaying isolated disturbance of the heparin-AT-III reaction. They classified this abnormality as Type III. Type II variants in their system were characterized by reduced progressive thrombin inactivating and heparin cofactor activities. The heterogeneity of this latter group became obvious very soon. In 1980, Sørensen et al. (7) described a variant AT-III with an isolated disturbance of the active center of the molecule. The direct comparison of the two variants ("Budapest" and "Aalborg") demonstrated the distinct entities of these two pathological AT-III molecules (8), although both belonged to Type II AT-III deficiency. At the same time we had the opportunity to study two Type I AT-III deficient families with different AT-III patterns on the heparinized CIE system: we designated Type 1a deficiency characterized by the normal pattern, and Type 1b the abnormal one (2). Taking into account these findings, we felt the classification system of Nagy et al. to be outdated and proposed our own in 1984 (9). In this system we defined two main categories: Type 1 (or quantitative) and Type 2 (or qualitative). Both classes were subdivided: Type 1a and 1b as described above, Type 2a was characterized by a profound change of the molecule, variably reflected in reduced serpin activity, abnormal heparin-AT-III reaction and aberrant immunochemical structure (e.g. AT-III "Budapest"), Type 2b by the isolated low serpin activity (e.g. AT-III "Aalborg") and Type 2c by the isolated abnormality of the heparin-AT-III reaction (e.g. AT-III "Paris"). This system has been accepted and used by several authors because the newly described variants could be fit into this system.

Nothwithstanding, on account of the development of methodology, a further revision of this classification system seemed necessary. Investigating the Type 1 AT-III deficiencies with isoelectrofocusing and immunoblotting, some qualitative abnormalities could be observed, too, independent from the heparin-AT-III reaction (10, 11). Type 1b subclass proved to be too narrow for classification of all the variants exhibiting low AT-III antigen level and a qualitative abnormality. Analyzing all the variants described, we proposed and improved simple classification system, mainly for clinical purposes (12).

Briefly, Type 1 (quantitative) AT-III deficiency includes the cases in which qualitatively normal AT-III is synthesized but at a reduced rate.

In Type 2 (qualitative) AT-III deficiency abnormal AT-III molecules are synthesized, but the level of AT-III antigen is normal in the plasma of the affected patients. Subtypes 2a, 2b and 2c can be differentiated as it has been described above.

In Type 3 (quantitative and qualitative) AT-III deficiency, at low AT-III antigen level abnormal AT-III molecules are synthesized. In addition to the variants previously denoted Type 1b, the other variants with showing abnormal patterns by isoelectrofocusing and immunoblotting etc. belong to this class.

We suggest to designate with toponyms only the abnormal AT-III variants, indicating the belonging to the classification system and the exact genetic defect (if it is possible). E.g., AT-III Budapest 1 (Type 2a), AT-III Toyama (Type 2c arg → cys^{47}), AT-III Utah (Type 3, pro → leu^{401}).

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