Renal Diseases, Disseminated Intravascular Coagulation, and Antithrombin III

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Dear Sir,

A recent article [1] and a letter [2], of which we became aware at its appearance in Nephron, prompted this reply. Both groups of authors have related their observations to an article [3, 4] in which we described a female with post-partum haemolytic uremic syndrome (PPHUS), as defined by Strauss and Alexander [5], complicated with severe disseminated intravascular coagulation (DIC), according to the definition of Spew et al. [6], and treated with infusion of antithrombin III (AT-III) concentrate.

Our comments upon the article by Monnens et al. [1] can be relatively brief. The authors document that DIC (as defined by Spero et al. [6]) is uncommon in epidemic HUS in children. This observation is by no means surprising, since it is well known that the prognosis, even without specific treatment, is good. We have examined only few children with HUS, and none of them had severe DIC and/or AT-III deficiency. A minor, but important mistake in the paper should be corrected. The major reason why AT-III deficiency is regularly found in DIC [e.g. 3, 4, 6–13] is not due to consumption of AT-III, but due to its trans-ferral to a 'receptor', which acts like heparin, and which is integrated in the surface structures of the cells, and becomes activated, when serine proteases (thrombin in particular) are generated and heparin neutralizers (platelet factor 4 in particular) are secreted into plasma [14]. Observations and interpretations consistent with this concept are available [8, 12, 15–19].

Monnens et al. [1] conclude that it is unnecessary to use AT-III concentrate in the treatment of HUS in children, since all their patients survived without such treatment, and as reflected in their estimations of AT-III levels in plasma. We agree with this conclusion.

Chester and Preuss [2] claim that our patient did not have a severe form of HUS with high mortality rate. However, in our research in the literature around 1979, when the article was written, we used much effort to define as accurately as possible 'a population', which had symptoms similar to our patient. Strauss and Alexander [5] described 'idio-pathic' PPHUS as (1) classical symptoms after delivery, and (2) not due to any identifiable causes including severe preeclampsia-eclampsia. Therefore, it was irrelevant in the classification of our patient that she had (1) increased serum creatinine before delivery, detected by routine screening, (2) slight pre-eclampsia before delivery, which was normal. We did not fail to report that the first evident symptoms of HUS developed after delivery and normalization of blood pressure. Furthermore, the syndrome of DIC in our patient developed after removal of a source, which can trigger such a complication – e. g. placental injections of thromboplastin during labour [e.g. 12]

– in predisposed patients, who, such as our, had a family history of thrombo-embolic diseases [3]. We therefore had to conclude that our patient had PPHUS according to the definition by Strauss and Alexander [5] and a bad prognosis (mortality 61 %). We still consider it most likely that the rapid recovery without kidney pathology (day 10) resulted from the use of AT-III concentrate.

Chester and Preuss [2] suggest that their patient may serve as a control. Although, by definition, the patient falls outside the group to which our patient belongs, a comparison might nevertheless be of interest.

Their patient had severe pre-eclampsia, progressing to eclampsia, which according to Strauss and Alexander [5] indicates symptomatic HUS, which has a much better prognosis than idiopathic 'PPHUS' [20]. Next, the patient received treatment, the efficacy of which we do not doubt (magnesium sulphate, diphenylhydantoin, and large doses of corticosteroid), all of which are known to stabilize the cell surfaces also in blood. Furthermore, corticosteroid accelerates the fibrinolysis in blood as already described by Fearnley [21] years ago, thereby preventing or diminishing the damage due to fibrin formation especially in the

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kidney, which is known to have a low level of plasminogen activator, and therefore is particularly vulnerable in DIC [22]. In conclusion, the patient reported by Chester and Preuss [2] does not represent a specific untreated control to our case.

This is confirmed by differences in the progression of the disease in the 2 cases. Chester and Preuss [2] reported a progression of the disease activity with a maximum of serum creatinine at day 6. In our patient, treatment with AT-III concentrate was started 26 h after delivery coincident with a maximum level of serum creatinine. Symptoms and signs related to hypoperfusion, such as vaso-constriction in the skin and confusions, disappeared within minutes (not reported previously) followed by a rapid normalization of the kidney function.

In our opinion, these data show that AT-III concentrate is a very efficient treatment, although – as already stated -it is difficult to compare the 2 patients. Thus, our results extend and verify the observations in chicken embryos [23] or in rats [24], in which AT-III prevents the toxic, thrombosis-inducing effects of thromboplastins, i. e. disseminated intravascular coagulation.

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