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Severe hemophilia A is caused by severe deficiency of factor VIII in the circulation. To date, a large number of mutations have been described as a cause for severe hemophilia A. However, the distribution of these mutations worldwide is heterogeneous and little data exists on the profile of mutations in hemophilia patients from India. We and several other groups were interested in finding out whether coinheritation of a thrombophilia gene in a severe hemophilia patient modifies its clinical presentation and the findings were instructive. Though most of the workers agreed that coinheritation of factor V Leiden does modify the clinical severity of severe factor VIII deficiency, the relevance of other thrombophilia markers were not evaluated in greater depth. In addition, data on newer molecules like TAFI and TFPI involvement in modulation of clinical phenotype of severe hemophilia is meagre.

There are certain indications that hyperfibrinolysis is an important component in

Thrombohemorrhagic balance in hemophilia: implications for alternative therapeutic approaches

severe hemophilia patients. Detailed studies of thrombohemorrhagic balance in severe hemophilia patients are lacking and such studies may provide rationalization of alternative therapeutic option which may complement or supplement factor VIII concentrate therapy. Its major utility could be in developing countries like ours where more rational use of antifibrinolytic drugs in association with factor VIII concentrate therapy will be possible. In developed countries development of other therapeutic products which may behave like TFPI inhibitors and/or TAFI may also be helpful in managing a selective group of patients, for example, patients with inhibitors.

The study is planned to be carried out as follows:

- i) Nature of mutations in severe hemophilia A patients from India by direct automated DNA sequencing
- ii) Correlate the severity of the disease with a battery of thrombophilia markers inherited by these patients e.g. protein C, protein S, antithrombin III, factor V Leiden polymorphisms, prothrombin gene (G 20210 A), MTHFR gene (C677T) polymorphisms, EPCR 23 bp repeat polymorphism, HPA 1b polymorphism.
- a) Polymorphisms of genes controlling fibrinolysis i.e. TPA, PAI-1, TAFI
- b) Gene polymorphism of factor XIII which helps in stabilization of clot and factor XIII levels in plasma
- c) Fibrinogen gene polymorphisms
- d) Polymorphism of tissue thromboplastin gene leading to its higher expression on monocytes

The antigenic as well as the functional protein levels in all these cases will be

studied.

The thrombophilic markers profile is expected to provide us with a fair idea of the strength of various genetic abnormalities and polymorphisms in modulating the clinical phenotype of the disease by “multivariate analysis program” using SPSS-6 software package. This information will be used to define a strategy for optimum day-to-day management of severe hemophilia patients .

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The thrombophilic markers profile will provide us with an indication of the potential of various genetic abnormalities and polymorphisms to modulate the clinical phenotype of hemophilia

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