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Current diagnostic and management strategy for childhood idiopathic thrombocytopenic purpura in Japan

Kohji Fujisawa

Department of Pediatrics, Jikei University School of Medicine

Idiopathic thrombocytopenic purpura (ITP) is a relatively common hemorrhagic disorder characterized by isolated thrombocytopenia without any identifiable systemic disease and is classified as acute and chronic form according to the duration of the disease. Although it is widely believed that the autoantibody-mediated platelet clearance through phagocytic system exceeding platelet production in bone marrow causes thrombocytopenia, the lack of unequivocal way to distinguish ITP from other immune or non-immune thrombocytopenia makes it difficult clearly to discriminate clinical entities. Furthermore, possible alteration of megakaryocytic maturation and subsequent platelet production evidenced by the lack of elevation in the value of serum thrombopoietin, which is the major regulatory factor of thrombopoiesis and is markedly increased in subjects with bone marrow failure such as aplastic anemia, also indicates “mixed” pathophysiology of ITP. Thus ITP seems to be a heterogeneous disorder.

On the other hand, even with newly developed protein-specific autoantibody test, the sensitivity and specificity of a positive autoantibody such as anti GPIIb/IIIa and Ib/IX antibody in the diagnosis of childhood ITP is up to 80%. Furthermore, these assays for specific autoantibodies have little or no essential diagnostic value especially for those with “childhood acute ITP” because typical abrupt onset often preceded by viral illness with no symptom other than bleeding unanimously leads to diagnosis of ITP. For that reason, specific etiological diagnosis of ITP has not been considered as necessary and, consequently, majority of childhood ITP remains to be an “idiopathic” disease

and is still heterogeneous. It may be partly because treatment will not always accurately target underlying mechanism responsible for thrombocytopenia that each therapeutic option including splenectomy currently used in the management of ITP is limited in its efficacy. Now that antigen-specific antibody test or specific antibody-producing cell assay has been developed, a subgroup of ITP patients with positive results should be defined as having “immune” thrombocytopenic purpura not as idiopathic. It seems to be of importance to classify ITP children according to causative factors for better analyzing heterogeneity of ITP and identifying new selection criteria for future therapeutic and non-therapeutic trials.

The management of childhood ITP differs worldwide concerning observation only, induction of specific treatment, bleeding symptoms and platelet counts. And the optimal treatment strategy is still a matter of controversy also in Japan because it is based predominantly on opinion rather than on evidence-based clinical approaches. Childhood ITP including those defined as having chronic disease has benign, self-limiting nature and the incidence of life-threatening hemorrhage such as ICH is very low. So most hematologists formally agree with taking non-treatment policy for patients with mild clinical symptoms and severe thrombocytopenia. But probably for the fear of unpredictable ICH, and preference of parents for specific treatment, many pediatricians including even hematologists practically incline to induce specific platelet-raising treatment. Furthermore, it is also reported that management strategy is different among hospitals and doctors. That is the reason for which the standardization of management is needed.

In the year of 2001, ITP committee in the Japanese Society of Pediatric Hematology mailed a questionnaire to all members asking how they would respond to hypothetical clinical situations of newly diagnosed ITP. Of clinical scenarios, children 18 months and 5 years of age with various platelet count were presenting either simple or wet purpura in questionnaire. For a child with his platelet count of $3,000/\mu\text{L}$, almost all respondents expressed will to administer specific platelet-raising treatment such as IVIg, irrespective of presence or absence of wet purpura nor number of ITP cases they have seen. On the contrary, for the scenario on a child with his platelet count of $16,000/\mu\text{L}$, it was shown that the absence of wet-purpura makes many respondents wonder whether to treat specifically, choosing no treatment in about 40%. In this situation respondents who have many ITP cases of practice tended to choose no treatment. These results showed that respondents, pediatric hematologists in Japan, formally supported no-treatment policy for ITP with mild clinical symptoms when platelet count is more than $10,000/\mu\text{L}$.

Apart from this survey, 498 eligible children with newly diagnosed ITP were enrolled between January 2000 and December 2002 from 84 nation-wide institutes to a registry established by ITP committee, through which clinical data concerning management and natural history were collected. These data represents practical management for childhood ITP within Japan.

In this survey childhood ITP had mainly developed below 5 years of age with incidence of male sex predominance. The initial platelet count was less than $10,000/\mu\text{L}$ in about two-thirds of cases enrolled, approximately half of which presented wet-purpura. Major bleeding at presentation was reported in 5 cases including one with ICH who died against intensive treatments. Children with their platelet count less than $10,000/\mu\text{L}$ were almost unexceptionally treated specifically with either IVIg or steroids or both, and preferably with IVIg in cases with wet purpura. Children rarely received parenteral or oral dose-escalating steroids in Japan. Even for those with presenting platelet count of $10,000$ - $29,000/\mu\text{L}$,

more than 80% of children received specific treatment including IVIg, steroids or both. Thus, rather intensive treatment strategy possibly for the fear of severe hemorrhage has been practically chosen for childhood ITP in Japan despite many pediatric hematologists formally agree with non-treatment policy for patients with mild bleeding symptoms as mentioned above.

Of those 498 children with newly diagnosed ITP 82 became chronic as defined by persistent thrombocytopenia more than 6 months from the onset while 416 children were defined as resolved acute ITP in no association with any treatment initially induced. Chronic ITP was seen in equal numbers of boys and girls mainly with insidious onset. Eight (9.7%) out of 82 chronic ITP children underwent successful splenectomy according to local practice during the follow-up period ranging from 6 to 41 months. Of the remaining 74 subjects unsplenectomized, 23(31%) were still under specific treatments while 52(70%), 34(46%) and 15(20%) had achieved platelet count of 50,000, 100,000, and $150,000/\mu\text{L}$, respectively, under condition of no treatment. Although it is difficult in this study to clarify indication for and general outcome after splenectomy, according to our experience of more than 100 children with prolonged, symptomatic and refractory thrombocytopenia, long-term response defined as achieving a platelet count of $>50,000/\mu\text{L}$ occurred in more than 80%. However, splenectomy was carried out less frequently in the recent cases including this study than in the earlier cases.

Children with newly diagnosed ITP proved to take a short and uneventful course of illness and high rates of subsequent remission are also predicted even for those with chronic disease. It still remains unclear whether natural course of childhood ITP is actually represented and whether prophylactic use of IVIg and other options may significantly reduce the risk of major hemorrhage as well as life-threatening ICH because true outcome of childhood ITP may be masked by specific intervention induced in majority of cases. In this regard, we believe that a child with ITP may be qualified to be treated specifically when his platelet count is markedly decreased

until a more reliable indicator to better identify severe bleeder comes to light. The accumulated experience obtained from prospective use of prophylactic IVIg, steroids and other options may help resolve this issue.

Taking these results into account, consensus guidelines for diagnosis and management of childhood ITP in Japan is being developed to standardize management and subsequently to reduce the rate of intervention by more selective treatment strategies firstly without compromising patients' safety.