Three Decades of Experience in Managing Immune Thrombocytopenia in Children in Arab Countries

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There are scattered and limited data in the literature on immune thrombocytopenia (ITP) in children from the Arab region. The aim of the current review is to present data from this region on the diagnosis, therapy, and morbidity associated with ITP. The first report was published three decades ago. It was assumed that there was a different disease pattern of ITP, but this was later discovered to be inaccurate and the frequencies of different ITP patterns were not different from other regions. The initial work-up for diagnosis of newly diagnosed ITP included routine bone marrow evaluation for all patients in most studies; however, a limited need for bone marrow for the initial evaluation was reported. An Egyptian multicenter study on the morbidity and mortality of intracranial hemorrhage (ICH) with other sporadic data was reported. Neither regional nor national guidelines for ITP management in most Arab countries have been reported. However, the use of initial intravenous immunoglobulin (IVIG) therapy in the Arabian Gulf region in contrast to corticosteroids in most other countries was obvious. Limited data on the use of anti-CD20, avoidance of unnecessary splenectomy, and the use of thrombopoietin receptor analogue in chronic ITP were published recently. A unified consensus for ITP management in the Arab region is essential but not yet realistic. More publications from this region are needed.

Semin Hematol 50:S22–S25.

Three-hundred sixty million people live in the Arab world: one third in Asia and two thirds in Africa. Genetic blood disorders are quite prevalent in this region because of the high rate of consanguinity. Regarding the acquired disorders as of immune thrombocytopenia (ITP), there are scattered data in the literature over the last decades from this region and most of the published studies are retrospective. Some national centers have joined the International Cooperative ITP Study Group (ICIS) registry on an individual basis.

EPIDEMIOLOGY

ITP is a heterogeneous disorder with a diverse natural history and diverse pattern of treatment response.[1] Previously known as idiopathic thrompocytopenic purpura and immune thrombocytopenic purpura, now ITP refers to ''immune thrombocytopenia.''[2] The first report on ITP in the Arab world was a retrospective study in 1981; they suggested that ITP patterns in Arabs could be different from the rest of the world, with more than 45% chronicity of ITP in four Arab countries.[3] A more recent retrospective report from Lebanon indicated a much lower chronicity rate of 10% (patients not achieving remission by 6 months).[4] Khalifa et al reported in a large Egyptian study a 30% rate of chronic ITP, matching the international reports.[5] This result has been confirmed by a more recent study.[6]

There was no gender preference in most acute ITP studies; however, chronic ITP was more frequent in females in Egypt.[6] In contrast, reports from the Arabian Gulf region[7,8] and Lebanon[4] have shown that nearly 80% of patients with chronic ITP were males.

A history of preceding viral infection was common in both acute and chronic ITP cases (71% and 63%, respectively).[7] A study from Emirates on 97 patients with ITP reported a history of upper respiratory tract infection 10–15 days prior to development of ITP in most of the studied cases.[8] A Lebanese prospective study showed that one third of their 50 patients had received immunization 2–8 weeks prior to the development of ITP.[4] A mass measles/mumps/rubella

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Publication of this article was supported by the International Cooperative ITP Study Group (ICIS).
Conflicts of interest: none.
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0037-1963

http://dx.doi.org/10.1053/j.seminhematol.2013.03.019

(MMR) vaccination for Egyptian secondary school adolescents after an epidemic of German measles in 2007 was followed by an increased incidence of ITP in the following few weeks.[9]

CLINICAL MANIFESTATIONS

The most common presentation of ITP was ecchymosis and petichae in 80%–100% of cases. However, absence of purpura does not exclude subclinical disease.[2] Hematemesis is a rare manifestation, being present in none of the subjects in the Emirate's report[8] and in 2% in the Egyptian study.[6] Similarly, hematuria was reported in two Lebanese children (4%).[4] It could be a warning sign for an associated intracranial hemorrhage (ICH).[10] Epistaxis is a common problem in pediatric ITP; it was reported in 10% of these patients in the Kuwaiti series.[11]

Ten cases of ICH were identified among children with ITP over a period of 10 years in five Egyptian centers: four patients had acute ITP, two persistent ITP, and four chronic ITP.[10]

Patients with secondary ITP are less likely to bleed than those with primary ITP and might have higher platelet count at diagnosis. This could be associated with evidence of a different or combination of autoimmune diseases.[12]

Splenomegaly is not a common feature of primary ITP; however, a Kuwaiti group reported a high prevalence of splenomegaly in 31 (55%) of 56 Arab children with ITP. They attributed this finding to the higher prevalence of sickle cell disease in their patients.[11]

The mortality rate of ITP is very low in Arab countries, matching the international standards of less than 1%. Death was due to ICH in one case in the Emirates study,[8] two children in the Egyptian study,[10] and in one patient in a report from Tunisia.[13]

WORK-UP

Most of the Arab reports over the last three decades have emphasized that initial laboratory evaluation for a child with typical acute ITP should include a complete blood cell count with a good peripheral blood film evaluation by an expert. It is unnecessary to request viral serology or autoimmune work-up, especially with no clinical evidence of a collagen vascular disease in children younger than 10 years of age. However, exclusion of secondary ITP is essential in adolescents with ITP.[10]

Almost all Arab children with ITP had undergone bone marrow examination to exclude malignancy or marrow aplasia.[7,11] The author of this report suggests that it was overdone and it is unnecessary for the initial evaluation of a typical newly diagnosed ITP presentation in children.[10] Therapy refractoriness or poor response to first-line ITP therapy should warrant a review of the diagnosis and a bone marrow examination.[14,15]

MANAGEMENT

The management of ITP in children is not uniform in the Arab world. It ranges from observation, medical treatment depending on bleeding symptoms, acceptable platelet counts, and availability of hospitalization or outpatient treatment.[10,16]

Admission to hospital is a common practice in Arab countries, particularly in patients with platelet counts $<20 \times 10^9$/L regardless of bleeding symptoms.[6–8,11,12] However, less than 10% of children with acute ITP are admitted in Egypt nowadays.[6]

Definitions of complete response (CR), partial response (PR), and no response (NR) vary dramatically in among studies from the Arab region.[6,8,11,12,16] We suggest to follow a uniform and clear definition of the response to therapy based on the recently published American Society of Hematology (ASH) guidelines.[17]

In the Arab region most children with ITP with platelet counts $<20 \times 10^9$/L initially received some form of platelet-enhancing treatment. In the Arabian Gulf countries the initial management consists mainly of intravenous immunoglobulin (IVIG) given at a dose of 1 g/kg/d for 2 consecutive days.[7,8,12] A cheaper alternative is RhoGAM (anti-D immunoglobulin [Bio Products Laboratory, UK]) at 50–75 mg/kg in a single dose. However, this treatment is less widely used.[18]

In the rest of the Arab countries, these patients are initially treated with some form of corticosteroid therapy either intravenous methyl prednisolone 10 mg/kg/d for 2 days[9] or 30 mg/kg/d for 3 days, or conventional prednisone 2 mg/kg/d for 2–4 weeks.[10] The author attributes this difference in practice, to the difference in the national income, which is higher in the Arabian Gulf countries and to the absence of national and regional guidelines. In Egypt many centers follow the international guidelines.[10]

There are no published studies on management of chronic ITP in children in the Arab world except an interesting prospective Omani study. The authors reported long-term remission in almost 50% of 13 refractory chronic ITP patients after 6 monthly courses of pulsed oral dexamesathone 40 mg/m^2 for 4 consecutive days.[16]

The management of primary ITP in adults has changed with the advent of anti-CD20 (Rituximab [Mabthera, Roche, Switzerland]) and thrombopoietin receptor agonists.[19,20] According to the ASH

guideline, Rituximab is considered as second-line therapy in patients who do not respond to corticosteroids and have repeated bleeding. A recent report from Oman described the successful treatment with Rituximab of an adult female with coexistence of ITP and idiopathic membranous glomerulonephritis.[21] In unpublished data, CR was reported in 25%, PR in 25%, and NR in 50% of 12 chronic refractory Egyptian children with ITP who received four courses of anti-CD20 (Rituximab) 375 mg/m^2 intravenously.

Splenectomy continues to induce the highest remission rate of chronic refractory ITP. (60%–70% at 5+ years).[19] There are few publications on its use in the Arab world. Four Kuwaiti patients were treated by splenectomy, and it was successful in three cases (75%).[11] In a retrospective study in Iraq, 40% of chronic ITP adults had splenectomy with an almost 80% remission rate.[22] During the period 1980–1998, 112 Egyptian patients with chronic ITP were splenectomized; at 5 years, 44 (45%) remained in CR and 34 (35%) in PR.[23]

Thrombopoietin receptor agonist was reported in only two publications from Egypt. A case series study revealed a variable response rate in children with chronic ITP treated with this category of drugs.[24] Ten of 12 patients (83.3%) on Romiplostim (Amgen, CA) treatment maintained the efficacy defined as an endpoint of platelet count $>50 \times 10^9$/L. Romiplostim was well tolerated and efficient in treating the children with chronic refractory ITP with no reported unexpected adverse events.[25]

CONCLUSION

Most of the studies and published reports on ITP from the Arab world are retrospective and there are few multicenter studies, even within the same country. Collaborative groups between centers managing children with ITP in this region are lacking and their creation should be encouraged. Moreover, standardization of practical guidelines for management of ITP in the region is needed.

Acknowledgments

The author thanks Professors Thomas Kühne and Paul Imbach from Basel University and the ICIS, and Professor Yasser Wali from Sultan Qaboos University, for critical review of the manuscript.

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