

Transfusion-Dependent Anaemia of Undetermined Origin: A Distinctive Syndrome in Paediatric Medical Tourism

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Abstract

Introduction: The underlying diagnosis of severe anaemic illnesses in children may not be easy to identify at times, especially when regular blood transfusion has been started. **Materials and Methods:** International children patients attending a haematology clinic for diagnostic evaluation were identified retrospectively if they had to receive repeated blood transfusions with an undiagnosed illness or an incorrect diagnosis. Their demographic data, presenting features, and eventual diagnosis were described. **Results:** Twelve children including 7 boys were enrolled from March 2007 to August 2011. Five came from Vietnam; 2 each came from Bangladesh and Indonesia; and 1 each from Hong Kong, Myanmar, and Ukraine. Their illnesses started at a mean age of 1.5 years (0.1 to 6.6) and they had been receiving blood transfusion for a mean duration of 2.5 years (0.1 to 9.9) years prior to the evaluation. Thalassemia major was the first diagnosis in 5 cases; one had been treated for autoimmune haemolytic anaemia while the rest had not been given a diagnosis. After the evaluation, 4 children were diagnosed with Diamond Blackfan anaemia, 3 were diagnosed with hereditary spherocytosis, and one each with hereditary pyropoikilocytosis, congenital sideroblastic anaemia, congenital thrombotic thrombocytopenic purpura, transient erythroblastopenia of childhood, and autoimmune myelofibrosis associated with human immunodeficiency virus infection. **Conclusion:** A definitive diagnosis can be identified in this cohort of children on medical tourism with severe anaemic illnesses requiring repeated transfusions with diagnostic approaches that circumvent the interference of transfused cells.

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Key words: Child health services, Diagnostic errors, Diamond Blackfan anaemia, Hereditary spherocytosis

Introduction

Childhood anaemia can either be a sign of haematologic disorders or as part of a multisystem disease. There are myriads of causes, which can be primary or secondary, inherited or acquired. A thorough medical history, including family history and perinatal events, physical examination, and a stepwise, logical approach to laboratory investigations are required to reach the underlying diagnosis. For children presenting with severe anaemia, a dilemma of arriving at an accurate diagnosis and starting blood transfusion treatment in time may be encountered. Once a blood transfusion has been given, further evaluation for the cause of anaemia may become more difficult. While general approaches to the diagnostic evaluation of anaemic children can be found in standard textbooks or review articles,^{1,2} strategies in

resolving diagnostic mysteries concerning children with severe anaemia who are already on blood transfusion treatment are lacking.

The Children's Haematology and Cancer Centre of Mount Elizabeth Hospital in Singapore has been receiving international patients for diagnostic and therapeutic purposes. A distinctive syndrome has been noticed among a group of children who come for a second diagnostic evaluation because of the need for repeated blood transfusion treatment. Their parents have not been given a clear diagnosis or they are doubtful of the original diagnosis. A retrospective review is therefore carried out to examine this group of children with transfusion-dependent anaemia of undetermined origin.

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Materials and Methods

This is a retrospective chart review from March 2007 to August 2011 from the Children's Haematology and Cancer Centre. Children were selected if they had an anaemic illness that required erythrocyte transfusion repeatedly for a duration of 4 weeks or longer, and the original diagnosis was either not clear or had to be revised after evaluation. The children's demographic data, clinical and laboratory features, and final diagnosis were described.

Children were evaluated systematically with the knowledge that transfused red cells might interfere with the interpretation of laboratory findings. After history taking and physical examination, all children were first screened with full blood counts, liver function tests, haemoglobin electrophoresis, direct Coombs test, and glucose-6-phosphate dehydrogenase deficiency. The peripheral blood film was examined with particular attention to a subpopulation of abnormal erythrocytes. If thalassemia was suspected, molecular screening for both α - and β -thalassemia mutations was sent. When erythrocyte membrane disorders were suspected, patients' red cells were sent for flow cytometry with eosin-5-maleimide labeling. If bone marrow failure syndromes or erythropoietic disorders were suspected, bone marrow aspiration and biopsy would be carried out. Other special tests were ordered based on the specific findings of individual patients.

Results

During the study period, there were a total of 26 children attending the clinic for consultation of a transfusion-dependent anaemia. Twelve cases were excluded as the final diagnosis agreed with the original finding. These included 4 cases of homozygous β -thalassemia, 4 cases of severe acquired aplastic anaemia, 3 cases of inherited bone marrow failure syndromes, and 1 case of autoimmune lymphoproliferative disorder. Another 2 cases were excluded as the final diagnosis did not differ from the original diagnosis significantly. The diagnosis was modified to Fanconi anaemia from acquired aplastic anaemia in 1 case and from homozygous β -thalassemia to haemoglobin E- β -thalassemia in another case. In none of the thalassemic patients was haemoglobin electrophoretic finding useful to clarify the diagnosis, which eventually had to be established based on the molecular results.

Twelve children, including 7 boys and 5 girls, were selected. Their anaemic illness started at a mean age of 1.5 years, ranging from 1 month to 6.6 years of age. At the time of second evaluation, their mean age was 4 years, ranging from 7 months to 10.3 years. The duration of transfusion treatment averaged 2.5 years, with a range from 1 month to 9.9 years. The lowest haemoglobin recorded was at a

mean of 4.8 g/dL (range, 2.3 to 7.8). Five children were originally given a diagnosis of thalassemia major, one with autoimmune haemolytic anaemia, and the rest came with no specific diagnosis. The final diagnosis after the second evaluation included Diamond Blackfan anaemia in 4 cases, hereditary spherocytosis in 3 cases, and 1 case each of hereditary pyropoikilocytosis, congenital sideroblastic anaemia, congenital thrombotic thrombocytopenic purpura, transient erythroblastopenia of childhood, and autoimmune myelofibrosis associated with acquired immunodeficiency syndrome. Three of these cases have been reported previously.³⁻⁵

History and Physical Findings

A history of severe neonatal jaundice requiring exchange transfusion was present in 2 cases, 1 with hereditary spherocytosis and the other with hereditary pyropoikilocytosis. A positive family history of severe anaemic illness was only elicited from a case of Diamond Blackfan anaemia. Associated congenital anomalies were found in two cases of Diamond Blackfan anaemia, one with intrauterine growth retardation and pre-axial polydactyly and the other with isolated central cleft palate. Splenomegaly was present in all the patients with haemolysis and was distinctively absent in patients with congenital or acquired pure red cell aplasia. Splenomegaly was however found in a child with Diamond Blackfan anaemia who also manifested myelodysplasia in the bone marrow.

Laboratory Findings

A summary of the clinical and laboratory findings is presented in Table 1. Direct examination of the peripheral blood film was the most helpful screening test in this group of children with transfusion-dependent anaemia. The presence of a moderate amount of microspherocytes identified 4 children who also tested positive on the flow cytometry with eosin-5-maleimide labeling. They were thus diagnosed with either hereditary spherocytosis or hereditary pyropoikilocytosis even though there had not been any positive family history. Two of them subsequently underwent splenectomy with restoration of normal haemoglobin level and freedom from further blood transfusion. Two of these children had been tested with osmotic fragility test in another institution after the commencement of blood transfusion therapy but the results were reported as normal. The finding of microangiopathic anaemia with thrombocytopenia in the presence of normal clotting screen led to the diagnosis of congenital thrombotic thrombocytopenic purpura in one child,⁴ whereas the presence of leukoerythroblastic blood picture led to the diagnosis of myelofibrosis secondary to acquired immunodeficiency syndrome in another child.⁵ A

Table 1. Clinical and Laboratory Features of Children with Transfusion-Dependent Anaemia

Case	Sex	Country of origin	Age (years) at		Diagnosis		Hb (g/dL) at		Thal DNA Test	Peripheral blood film findings	Remarks
			First	Final	First	Final	Lowest	Final			
1	Boy	Vietnam	0.1	1.4	AIHA	HPP	4.8	8.1	ND	Burn-like	Positive test for EMA (– 26.9%)
2	Boy	Vietnam	0.1	0.6	Nil	HS	3.4	8.2	Neg	Spherocytic	Positive test for EMA (– 17.4%); Remitted after splenectomy
3	Boy	Ukraine	0.2	8.0	Nil	DBA	4.3	9.4	ND	Neutropenic	Marrow red cell hypoplasia and dysplasia
4	Girl	Vietnam	0.4	10.2	Thal	DBA	6.0	10.0	ND	Non-specific	Marrow red cell hypoplasia
5	Girl	Vietnam	0.5	1.6	Thal	DBA	7.8	7.6	Neg	Non-specific	Marrow red cell hypoplasia
6	Girl	Indonesia	0.8	1.0	Thal	HS	4.0	8.6	Neg	Spherocytic	Positive test for EMA (– 19.9%); Remitted after splenectomy
7	Boy	Bangladesh	0.8	1.7	Nil	USS	4.0	4.6	ND	Microangiopathic	ADAMTS13 absent
8	Boy	Indonesia	0.8	1.1	Nil	MF	6.2	6.3	ND	Leucoerythroblastic	Marrow fibrosis
9	Boy	Hong Kong	1.6	1.7	Nil	TEC	2.3	2.3	ND	Non-specific	Marrow red cell aplasia
10	Girl	Myanmar	2.8	6.9	Nil	HS	5.0	8.2	Neg	Spherocytic	Positive test for EMA (– 16.6%)
11	Boy	Vietnam	3.6	4.2	Nil	DBA	5.0	9.7	Neg	Non-specific	Marrow red cell hypoplasia
12	Girl	Bangladesh	6.6	10.0	Thal	CSA	5.0	7.1	Neg	Microcytic	Marrow ringed sideroblasts

ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AIHA: autoimmune hemolytic anaemia; CSA: congenital sideroblastic anaemia; DBA: Diamond Blackfan anaemia; EMA: flow cytometry with eosin-5-maleimide, percentage reduction in mean channel fluorescence in parentheses; Final, second evaluation: First, first/original evaluation; HPP: hereditary pyropoikilocytosis; HS: hereditary spherocytosis; MF: autoimmune myelofibrosis; ND: not done; Neg: negative; TEC: transient erythroblastopenia of childhood; Thal: thalassemia; USS: Upshaw-Schulman syndrome (congenital thrombotic thrombocytopenic purpura)

haemolytic anaemia associated with microcytosis was found in a 10-year-old girl who had been treated as thalassemia but haemoglobin electrophoresis and molecular screen were negative. The diagnosis of congenital sideroblastic anaemia was established on bone marrow aspiration.³ In 4 children, the peripheral blood film did not reveal any specific features except for the distinct absence of polychromasia. Erythroid hypoplasia or aplasia was found on bone marrow aspiration and biopsy. Diamond Blackfan anaemia was diagnosed in 3 of them while the fourth child recovered after 6 weeks, fulfilling the diagnosis of transient erythroblastopenia of childhood. Chromosome fragility test was negative for the 3 cases of Diamond Blackfan anaemia.

Discussion

Children with severe anaemic illnesses who are already on blood transfusion therapy present a unique problem in medical tourism. Most of them come from the developing countries where thalassemic syndromes are prevalent. Important clues to the underlying diagnosis might have been ignored and/or pertinent tests are not available to allow for comprehensive diagnostic evaluation. Once blood transfusion therapy has been commenced, attempts to clarify diagnostic uncertainties become more difficult. The findings on haemoglobin electrophoresis, assay of red cell

enzymes including pyruvate kinase, and osmotic fragility test are difficult to interpret or unreliable in the presence of transfused allogeneic blood cells.

In children presenting with transfusion-dependent anaemia with undetermined origin, examination of the peripheral blood smear remains a powerful tool to guide further diagnostic strategies. The presence of polychromasia, often accompanied by basophilic stippling and nucleated red cells, is often a good indicator for haemolytic anaemia, consumptive disorders, and ineffective erythropoiesis. In contrast, its absence is often indicative of a marrow failure syndrome and hence the need for bone marrow examination.

Even though blood transfusion may have ameliorated the florid microscopic features of the underlying disease, a careful search for abnormal size and shapes of the remaining host cells is still fruitful in the majority of cases. Hereditary spherocytosis, a collective condition associated with disordered erythrocytic cytoskeleton associated with abnormal structural proteins including spectrin, ankyrin, protein 4.2 and band 3, appears to be a commonly missed diagnosis in this group of children. The absence of a dominant Mendelian inheritance in the affected families and the negative result from osmotic fragility test after the commencement of blood transfusion therapy may have confused the diagnosis from the original countries.

In such cases, a positive finding on eosin-5-maleimide fluorescence-labeled flow cytometry serves as a strong supporting evidence for hereditary spherocytosis and related disorders, as eosin-5-maleimide binds specifically to band 3, Rh-associated glycoprotein and CD47, which are integral proteins in close association with the red cell cytoskeleton.⁶

Since thalassemia is still the commonest haematologic disorder requiring regular blood transfusion treatment in childhood, it is perhaps not surprising to see children misdiagnosed with thalassemia major if they present in early infancy or if there is microcytic anaemia associated with haemolysis.³ On the other hand, as the majority of children in this series originated from thalassemia endemic areas, and thalassemic conditions may co-exist with other haematologic diseases, molecular means for the diagnosis or exclusion of thalassemia is still commonly employed as part of the evaluative strategy. Findings from haemoglobin electrophoresis have not been informative after regular blood transfusion.

Conclusion

In summary, undiagnosed or misdiagnosed transfusion-dependent anaemia represents a unique clinical entity in paediatric medical tourism. A lack of expertise in paediatric haematology, diagnostic facilities, and failure to recognise atypical haematologic disorders are probable reasons for missing the diagnosis from their original countries. A systematic approach that circumvents the interference of transfused red cells is required to resolve the diagnosis.

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