Hypothetical Views On Some Unusual Disease Associations With Sickle Cell Anaemia

OT Adedoyin, OO Adesiyun, MA Adeboye and Femi Mark

Department of Paediatrics, University of Ilorin Teaching Hospital, PMB 1459, Ilorin, Nigeria

Summary

Sickle cell anemia (SCA) is a disease accompanied with several complications arising mainly from vasoocclusion and haemolysis. There are also complications of infections which may occur due to defective cell mediated and humoral immunity. However, there are associations that have been observed to be unusual in children with sickle cell anaemia from anecdotal experience. These include febrile seizure, malignancies, malnutrition, cerebral malaria, tuberculosis and connective tissue disorders. There are anticipated connections between some of these illnesses and SCA. However, the fact that they do not occur commonly, raise the probability that certain yet unknown factor in the sickle cell patient may be protecting these patients against them.

Keyword: Unusual, associations, sickle cell anaemia

Introduction

Sickle cell anaemia (SCA) occurs as a result of replacement of glutamic acid with valine on positon 6 of the beta chain of the adult haemoglobin. It is a disease that could be accompanied with several complications which arise due to vaso-occlusion and haemolysis. The complications affect virtually every organ in the body. Respiratory complications are acute chest syndrome and pneumonia while papillary necrosis of the kidney and myocardial infarction is an example each of urogenital and cardiovascular system complications.[1] However, there are also associations that have been noticed to be unusual in children with sickle cell anaemia. They are unusual to the extent that they are not explainable or even when they are explainable, they rarely occur or when they do occur it's just sporadic. Some of these unusual associations that have been observed in our practice include febrile seizure, malignancies, cerebral malaria, malnutrition, tuberculosis of the spine and connective tissue disorders. There are anticipated connections between these illnesses and SCA. However, they do not occur frequently fueling the probability that there may be some yet unknown factor in the sickle cell individual that protects against them. It may also be possible that nature does not allow double jeopardy in the same individual.

Correspondence to:

Dr OT Adedoyin
Department of Paediatrics
University of Ilorin Teaching Hospital,
PMB 1459, Ilorin, Nigeria
E-mail: ooadedoyin@yahoo.com

Febrile seizure

It occurs at the early period of life between the ages of 6months to 5years when the brain is not fully developed.[2-5] It is mainly secondary to febrile illnesses especially malaria in our endemic environment.[6-7] There is a strong family history of febrile convulsion in siblings and parents of children with this disorder.[5,8] Linkage studies in several large families have also mapped the febrile convulsion gene to chromosome 19p and 8q loci13-21, while the inheritance of febrile convulsions has been described as being compatible with transmission by a single dominant gene with incomplete penetrance.[9-11] Sickle cell anaemia patients are predisposed to developing febrile illness because of the inherent depressed immunity from reduced humoral and cell mediated immunity, functional asplenia and the available abundant iron storage which micro-organisms utilizes for growth.[1] They could therefore develop febrile illnesses as a result of infections ranging from malaria to bacteria infections. Children under the age of five years are liable to complications of a febrile illness such as febrile seizures. In our practice, which may have its own limitation, febrile seizures are not common occurrences in children with sickle cell anemia. This is not however the experience in Lagos, Nigeria where a 10.4% prevalence has been found among children with SCA. The study however left out children less than 4 years of age who are really critical for a study of that nature. The authors also unfortunately depended on the recall ability of the parents of this children as they administered questionnaires. This is fraught with errors as what they may assume to be a febrile seizure may actually be meningitis or other intracranial illness. We also wondered how febrile

seizure will be an issue beyond 5years of age as it is well established that seizure associated with a febrile illness in a child beyond the age of 5 years should be thoroughly evaluated for intracranial infection.[11] In a similar work carried out by Adeboye in lIorin, he found 6 children with haemoglobin SS and one child with Hb SC, in his cohort of 162 children with febrile seizure whose haemoglobin genotype were evaluated. However all the 7 children in his series with sickle cell anemia also had severe anemia (PCV<15). He could therefore not categorically state whether the seizure occurred as a result of fever or severe anaemia.[12] While their works constitute a good attempt at unraveling the occurrence of febrile seizure in SCA children , they have not convincingly enunciated the magnitude of the predisposition of SCA patients to febrile seizures. A hospital based study involving the analysis and confirmation of the genotype of all children with febrile seizure would be helpful. Such study must have an adequate sample size in both the control and the patients and confounding variables such as severe anaemia must be somehow eliminated.

It is suspected that just as the sickle cell trait protects against malaria, sickle cell gene may offer some protection against febrile seizures in children, not necessarily all forms of seizure disorders because studies have shown a 10.4% prevalence of epileptic seizures among children and adult with SCA. The reason for this protection may likely be genetic or due to some yet unknown factors present in sickle cell individuals, since vasculopathy and the focal hypoperfusion which occurs in SCA patients would favour the occurrence of a seizure.

Malignancies

Malignancies are common in children, with Burkitt lymphoma (BL) being the leading malignancy of African children. Others include nephroblastoma, neuroblastoma and acute lymphoblastic leukaemia (ALL).[13] BL is common in the malarial belt which is incidentally the area where the prevalence of SCA is high.[14] Despite the fact that these tumors are common in the general population, they have not been observed anecdotally in patients with SCA. Only a case of Hodgkin's lyphoma has been reported in the literature.[15] This rarity is difficult to explain since some of these lymphoma occur in the general population but hardly occurs in the SCA patients. The SCA patients also have favourable predisposing factors such as malaria, malnutrition, exposure to radiation, low socio-economic background (indeed most malignancies in the tropics occur in children of low socio-economic background).

It is likely that the sickle cell gene may provide protection against malignancies. Does the recurrent bone marrow stimulation due to anaemia protect against bone marrow malignancies? Or does the recurrent breakdown of red cells also help to destroy oncogenes? Does the vasoocclusion disrupt the flow and even destroy factors that aid oncogenic stimulation or does the chronic hypoxia inhibit the multiplication of oncogenic cells? All these remain to be elucidated.

Protein energy malnutrition

Protein energy malnutrition (PEM) is a leading cause of morbidity and mortality in the tropics. It occurs largely due to poverty, ignorance and multiplicity of infectious diseases that affect African children.[16] Many theories have been proffered by Hendrickse for the occurence which include aflatoxin and the free oxygen radical theories.[17] It is thought that the PEM state provokes the production of aflatoxin and free oxygen radicals which destroy the cells producing the pathology seen in PEM. Sickle cell anaemia patient may fail to thrive and look small for age compared to their counterpart without SCA but the typical PEM picture rarely occurs in them yet all the favourable factors such as inadequate intake of food due to recurrent illness occurs in SCA. It is postulated that the chronic hypoxia may destroy or inactivate the aflatoxin and free oxygen radicals. It is also possible that the extra attention paid to them in terms of care in order to prevent crisis may contribute to its rarity. The frequent hospitalizations in some of them also afford the physician the opportunity to avert major precipitant and causes of malnutrition.

Tuberculosis

Tuberculosis (TB) is caused by an acid fast bacilli (AFB) that has predilection for the lungs even though it affects several other organs in children. It is also a common cause of morbidity and mortality in children.[18] It is endemic in the tropics where SCA is most prevalent. Its prevalence in SCA patients compared to the general population is quite low and unremarkable. SCA patients are predisposed to infection due to depressed cell mediated immunity and functional asplenia. It is therefore thought that TB should occur commonly in SCA patients like in other

immunosuppressive illness like HIV. However, it rarely does. It is likely that the chronic hypoxia that obtains in SCA is unfavourable for the growth of AFB . However , they are susceptible to encapsulated organisms such as pneumococci which are also aerobic organisms. Probably the AFB needs much more oxygen than the pneumococcus. Studies have indicated a low prevalence of TB in children with SCA.

Most of the papers reporting TB in SCA patients were mainly in adults and were single case reports.[19-23] Only two previous studies had extensive reviews over a long period. In one of the studies where 166 hospitalized patients with SCA were reviewed for TB, only 5 cases were found(3 diagnosed by sputum and 2 by lymph node biopsy).[24] The second was in a cohort of 457 SCD patients seen over 8 years and only 12 cases off TB were seen. There were 7 lymph node lesions, 3 pulmonary lesions and 2 vertebral lesions.[25]

Cerebral malaria

Cerebral malaria (CM) is a severe form of malaria characterized by fever, convulsion and loss of consciousness with heavy parasitemia. It is a major cause of death in children in the tropics. Sickle cell anaemia due to their low immunity is highly susceptible and is more predisposed to the severe form of malaria including CM. However, while severe anaemia may occur, CM is not common in them. Studies have revealed that children with AS and AA haemoglobin genotypes are equally susceptible to CM. The study was however silent on the homozygous hemoglobin S gene.[26] Again anecdotal observation have indicated that CM is uncommon in children with SCA. This may be due to the fact that the parasitized red cells are quickly destroyed before they get into the cerebral circulation hence the major complication that may be experienced remain severe anaemia.

Connective tissue disorder

Connective tissue disorder is rare in the African population but it is even rare in SCA patients who develop similar features like bone and joint pains. Patients with SCD present with defective activation of the alternate pathway of the complement system that increases the risk of capsulate bacterial infection and failure to eliminate antigens predisposing these patients to autoimmune diseases.[27] in view of the similarity of symptoms except for the rash, the diagnosis of connective tissue disorder such as systemic lupus Erythematosus (SLE) could be delayed as symptoms are likely to be attributable to SCD than the connective tissue disorder. This is because of overlap of features of SCD with other chronic illnesses such as SLE.[27] There are only 23 reported cases of SLE occurring in patients with SCD in literature suggesting that the association is rare.[28]

The submission in this paper is a product of several years working experience among children with SCA. It is possible that this experience may be isolated, short sighted and narrow. Attempts have been made to peruse the literature to justify or debunk some of theses observations. However, they still look solid on ground and worthy of more extensive research all over the world. For instance, if our observations on the rarity of malignancies in SCA are valid, it may be plausible to investigate if a factor produced by patients with sickle cell anaemia could prevent malignancies or even CM, TB etc.

References

1. Olanrewaju DM. Complications of sickle cell anaemia-A review. Nig Med Pract 1988:16:107-111.
2. Ouellette EM. Convulsions. In Dersherwitz RA (ed.), Ambulatory Paediatric Care, Lippincott-Raven, New York, 1993: 578-580.
3. Levene M. Disorders of the nervous system. In Levene MI (ed.), Jolly's disease o f children. ELBS/Blackwell Scientific Publications, London1990: 284-286
4. Iloeje J.O. The impact of socio-cultural factors on febrile convulsion in Nigeria, West Afr. J.Med. 1989:8:54-58
5. Hirtz DG. Febrile convulsion. Pediatr Rev 1997:18: 5-8.
6. Fagbule D, Chike-obi UD, Akintunde EA. Febrile convulsions in Ilorin. Nig J Paediatr 1991; 18: 23-27.
7. Angyo IA, Lawson JO, Okpeh ES. Febrile convulsions in Jos. Nig J Paediatr 1997; 24:7-13
8. Haslam RA. Febrile convulsion. In: Behrman RE, Kliegman RM, Jenson HB eds. Nelson textbook of Paediatrics. WB Saunders Company, Philadelphia 2000:1813-19
9. Scott-Emuakpor AB, Longe AC. Some aspects of the genetics of febrile convulsion. Nig J Paediatr 1985:12:49-55
10. Camfield CS, Camfield PR. Febrile s e i z u r e s . M e d l i n e s e a r c h www.epilepsy.org/ctf/febrile convulsion. html.

Accessed on 6th October 2003:1-11.
11. Kehinde MS, Temiye EO, Danesi MA. Neurological complication of sickle cell aneamia in Nigerian African – A case-control study. J Natl Med Ass. 2008:100(4):394-399.
12. Adeboye MAN. Haemoglobin genotype and clinical profile of children admitted with febrile convulsion at the University of Ilorin Teaching Hospital, Ilorin Dissertation submitted to the National Postgraduate Medical College November 2006.
13. Johnson AOK, William CKO. A reappraisal of the management of common childhood abdominal malignancies in Ibadan. Nig J Paediatr 1984:11(2):29-39.
14. Familusi JB, Adeyokunnu AA, Folami AO, Ayeni O. Observations on the seasonal pattern of Burkitt's lymphoma in Ibadan. Ibadan. Nig J Paediatr 1981:8(1):16-23.
15. Brown BJ. Kotila TR. Hodgkin lymphoma in a child with sickle cell anaemia. Pediatr Haematol Oncol 2007:24(7):531-535.
16. Reddy V. Protein energy malnutrition. In : Stanfield P, Brueton M, chan M, Parkin M, Waterson T (eds.), Diseases of children in the Subtropics and Tropics, Arnold- ELST Publishers, London 2001 :357 :335-337.
17. Hendrickse RG. Protein eenergy malnutrition. In : Hendrickse RG, Barr DGD, Matthews TS (eds.). Paediatrics in the tropics. Blackwell Scientific Publications , London 1991 :119-131.
18. Shennan DH, Kibel MA. Tuberculosis. In : Stanfield P, Brueton M, chan M, Parkin M, Waterson T (eds.), Diseases of children in the Subtropics and Tropics, Arnold-ELST Pubblishers, London 2001 :357 :519-552.
19. Koffi N, Koffi KG, Sangare A. Prevalence de la tuberculose chez le drepanocytaire Africain. Rev Pneumol Clin 2000:56:219-220
20. Bowman SJ. Pulmonary tuberculosis precipitating the nephritic syndrome in a patient with sickle cell Disease. Nephron 1991; 57:236
21. Chan O, Love day E. Case report: Widespread tuberculosis in sickle cell disease. Clin Radiol 1992:45:211-4
22. Banerjee AK, Coltart DJ. Abdominal tuberculosis mimicking lymphoma in a patient with sickle cell anaemia. Br J Clin Pract 1990:44:660-661.
23. Ammar J. Ghrairi H, El-Mekki F, Aissa 1, Hamzaoui A. Acute chest syndrome in sickle cell disease: About 3 cases with review of the literature. Tunis Med J 2003:81:345-350
24. Barrett- Connor E. Bacterial infection and sickle cell anaemia. Medicine 1971:50:97-112
25. Lionnet F, Bachmeyer C, Sloma I, Rossier A, Thioliere B, Maier M, Grateau G, Givot R, Cadranel J. Tuberculosis in adult patients with sickle cell disease. Journal of Infections 2007:55:439-444.
26. Olumese PE, Adeyemo AA, Ademowo OG, Gbadegesin RA, Sodeinde O Walker O. The clinical manifestation of cerebral malaria among Nigerian children with the sickle cell trait. Ann Trop Paediatr 1997:17(2):141-145.
27. Appenzellers, Fattori A, Saad ST, Costallat LT. Systemic lupus erythematosus in patients with sickle cell disease. Clin Rheumatol 2008:27(3):359-364.
28. Ogunbiyi AO, George AO, Brown AO, Okafor BO. Diagnostic and treatment difficulties in systemic lupus erythematosus co existing with sickle cell disease. West Afr J Med 2007:26(2):152-155.