

RESEARCH ARTICLE

Open Access



Coexistent sickle-cell anemia and autoimmune disease in eight children: pitfalls and challenges

Valerie Li-Thiao-Te^{1*} , Florence Uettwiller², Pierre Quartier^{2,3,4}, Florence Lacaille⁵, Brigitte Bader-Meunier^{2,3,4}, Valentine Brousse⁶ and Mariane de Montalembert⁶

Abstract

Background: Patients with sickle cell disease (SCD) present a defective activation of the alternate complement pathway that increases the risk of infection and is thought to predispose to autoimmune disease (AID). However, coexisting AID and SCD is rarely reported, suggesting possible underdiagnosis due to an overlapping of the symptoms.

Study design: Among 603 patients with SCD followed between 1999 and June 2016, we retrospectively searched for patients with coexisting SCD and AID.

Results: We identified 8 patients aged from 7 to 17 years diagnosed with AID; juvenile idiopathic arthritis ($n = 3$), systemic lupus erythematosus ($n = 2$), Sjögren's syndrome ($n = 1$) and autoimmune hepatitis ($n = 2$). The diagnosis of AID was often delayed due to similarities of the symptoms with those of SCD. Patients treated with steroids experienced multiple vaso-occlusive crises and received prophylactic chronic blood transfusions when it was possible. Tolerance to other immunosuppressive and biological treatments, such as anti-TNF agents, was good. A remission of AID was achieved in 4 patients, without worsening the course of the SCD. One patient underwent a geno-identical hematopoietic stem cell transplantation that cured both diseases. Another one underwent a successful liver transplantation.

Conclusion: Coexistence of AID and SCD generates diagnostic and therapeutic challenges. Early diagnosis of AID is important to define the best treatment, which may include targeted biological therapy.

Keywords: Sickle cell disease, Autoimmune disease, Juvenile idiopathic arthritis, Systemic lupus erythematosus, Children, Biological therapy

Background

Sickle cell disease (SCD) is a common inherited condition in African, Caribbean, and Mediterranean countries. Production of abnormal hemoglobin S is responsible for the sickling of red blood cells in deoxygenated conditions. SCD manifests itself as chronic intravascular hemolysis, vaso-occlusion and painful crises. Over time, multiple organ damage can develop. Patients with SCD display a defective activation of the alternate complement pathway, leading to an increased risk of infection with encapsulated bacteria (*pneumococci*, *Haemophilus influenzae*) [1–3]. It

was suggested that complement abnormalities could predispose to autoimmune disease (AID) [4]. However, the frequency of coexisting SCD and AID has not been evaluated, and most data come from case reports [5–14]. Manifestations of AID, such as fever, polyarthritis, and multiorgan involvement, can also be caused by SCD, leading to a delay in diagnosing the AID [11]. Furthermore, antiinflammatory drugs such as steroids and immunosuppressive therapy used to treat AID can induce severe SCD complications.

Study design

Between 1999 and June 2016, 603 patients with SCD aged under 18 years were seen at the hemoglobinopathy reference center of the Necker Hospital, Paris, France.

* Correspondence: lithiaote.valerie@chu-amiens.fr

¹Onco-Hématologie Pédiatrique, Centre Hospitalier Universitaire Amiens, Amiens, France

Full list of author information is available at the end of the article



Among them, we searched for patients with coexisting SCD and AID.

We retrospectively collected data from the medical records of SCD patients followed in our institution, the largest Pediatric University-Hospital in France, which has a national reference center for SCD and a national reference center for pediatric rheumatology diseases. Started in 2007, data from the patients referred to the pediatric rheumatology team were registered in the CEMARA database, a nationwide web-based information for rare diseases [15] approved by the French patients Data Protection Authority (*Commission Nationale de l'Informatique et Libertés*, CNIL), after patients'/parents' information and verification of their non-opposition. In accordance with the French legislation, no ethics committee agreement was requested for such a retrospective survey.

Results

Among the 603 children with SCD followed between 1999 and June 2016, we identified 8 patients aged from 7 to 17 years, who developed an AID. All patients were Afro-Caribbean homozygous SCD (Hb SS) children either diagnosed by neonatal screening (patient 1, 6, 7 and #8) or during infancy (patient 2, 3, 4 and #5). The diagnoses were juvenile idiopathic arthritis (JIA, $n = 3$), systemic lupus erythematosus (SLE, $n = 2$), Sjögren's syndrome ($n = 1$) and autoimmune hepatitis ($n = 2$). These 8 patients received joint follow-up by hematologists, rheumatologists and an hepatologist. Table 1 reports the medical history before the diagnosis of the AID and the clinical and laboratory findings that led to the diagnosis of AID.

In one patient, SLE was diagnosed within a few weeks of the onset of the symptoms because of fingers swelling, not a common site of vaso-occlusion in adolescents with SCD. In another patient, alopecia and aphthous stomatitis helped diagnose the SLE several months after the first neurologic symptoms and polyarthritis had appeared. In some patients, the diagnosis was delayed for several years (Table 1). Before the diagnosis of JIA, patients #2 and #4 had had a long history of joint pain and ankle and knee swelling, first ascribed to SCD and treated as SCD complications (analgesics, hyperhydration, hydroxyurea for patient #2 and exchange transfusion for patient #4). Patients 5 and #8 displayed biological signs of liver dysfunction (elevation of AST and ALT, cholestasis). Liver biopsy showed lymphoplasmocytic infiltrates and mild fibrosis compatible with autoimmune hepatitis. For patient #7 diagnosed with SLE, cerebral MRI was performed in response to the worsening of neurologic symptoms and showed periventricular hyperintensity and cortico-subcortical atrophy compatible with lupus lesions. The tolerance to AID treatment was good. Among the 4 patients treated with steroids, 3 had a concomitant exchange transfusion program in order to

prevent vaso-occlusive crises and 1 received hydroxyurea. Red blood cell alloimmunisation in 1 patient required a switch from transfusion to hydroxyurea. Complete remission of the AID was obtained for 4 patients with a classical immunosuppressive treatment ($n = 1$), biological treatment ($n = 2$) or genodental hematopoietic stem cell transplantation ($n = 1$), although 1 patient (patient #4) had arthritis sequelae. Despite being associated with AID, the SCD course was stable for 5 patients. The patient who underwent stem cell transplantation was cured of both AID and SCD. Patient #4 who did not receive hydroxyurea or transfusion experienced several vaso-occlusive crises during the follow up. Patient #8 who underwent liver transplantation due to chronic infectious cholangitis, presented multiple post-transplant complications (rejection, biliary stenosis, high blood pressure, posterior reversible encephalopathy), but had a normal liver function and a much improved quality of life at the last follow up. Table 2 reports the treatments and last follow-up data.

Discussion

We report 8 cases of coexisting SCD and AID including polyarticular JIA and juvenile SLE in a cohort of 603 patients with SCD. The incidence of AID in France in an ethnic matched population is not known, as it is not allowed to compare diseases according to patients' ethnicity. These cases highlight the diagnostic difficulties raised by the symptom overlapping between AID and SCD (e.g., polyarthritis, anemia, and fever) and the therapeutic challenges. Nevertheless, the use of immunosuppressive drugs (except steroids), including new drugs such as TNF α antagonist was well tolerated and provided durable AID remissions, without worsening the course of the SCD when associated to specific SCD treatments.

AID such as SLE [16] and polyarticular JIA [17, 18] are more common in Blacks than in other ethnic groups. In addition to genetics, patients with SCD present functional asplenia and defective activation of the alternate complement pathway [1–4]. Although published data focused on functional complement abnormalities, it would be interesting to assess the impact of functional asplenia itself in the occurrence of AID [19]. However, the coexistence of AID and SCD seems to be rare, potentially underdiagnosed, and its prevalence is unknown. In a study of 30 patients with SCD and connective tissue disease, 15 patients (50%) had rheumatoid arthritis, 13 (44%) had SLE, 1 (3%) had Sjögren's syndrome, and 1 (3%) had scleroderma [20]. Most data on coexistent AID and SCD come from anecdotal case-reports [5–14] describing patients SLE [2, 8–11], or far less often, JIA [5–7] or autoimmune hepatitis [12–14].

Our patients reflect the diagnostic challenges of JIA in children with SCD. We report diagnostic delays from 1 to 8 years, as could be found in previous reports [5–7].

Table 1 Medical history, clinical and biological findings at presentation in our patients

Patient	1	2	3	4	5	6	7	8
Sex	M	M	F	M	M	F	F	F
Medical history related to SCD	ACS (3 episodes) Recurrent VOC	Recurrent polyarthralgia ^a	Recurrent VOC	Recurrent VOC Osteomyelitis right femur Chronic hepatitis B	Recurrent VOC Acute cholecystitis, <i>Salmonella</i> septicemia Bilateral avascular necrosis of femoral heads	Recurrent VOC	Recurrent VOC ACS (3 episodes)	Recurrent VOC ACS Acute splenic sequestration Recurrent cholangitis
Type of AID	SLE	JIA	JIA	JIA	AIH	Sjogren's syndrome	SLE	AIH
Age at onset of AID (years)	13	4	7	4	17	11	15	3
Age at diagnosis of AID (years)	13	13	7	6	17	13 (11 for initial diagnosis of JIA)	15	3
Symptoms	Asthenia, denutrition polyarthritides fingers and toes hepatomegaly pericarditis	Polyarthritides left knee and right ankle severe arthropathy at 10 y uveitis	Polyarthritides (temporo-mandibular arthritides and sacroiliitides)	Polyarthralgia bilateral knee arthritides Asthenia, weight loss	Polyarthralgia	Polyarthralgia (spine); knee arthritides; Secondary recurrent parotitides; xerostomia at 13 y	Polyarthritides; pleuritides, pericarditides, aphthous stomatitides, alopecia; pulmonary hypertension; behavior disorder	Hepatomegaly; jaundice
ESR (mm/h)	74	95	34	86	67	14	84	88
IgG (g/l)	38	26	–	–	35	23	30	26
ANA pattern	1/1280 homogeneous	1/160 speckled	Negative	1/80 homogeneous	1/80	1/1280	1/80 speckled	1/160
Others immunological features	Anti-DNA antibodies + (43 UI/ml) Coombs +	RF negative	RF positive		Anti-U1RNP + Farr test 29%	Anti-SSA, SSB + Anti-U1RNP + Antiβ2GP1 + Antiphospholipid antibodies +	Anti-DNA antibodies + (44 UI/l) pANCA Coombs + Antiplatelets antibodies + Antiβ2GP1 + anticardiolipin + Neutropenia	c-ANCA + Smooth muscle antibodies + (1/50)

VOC vaso-occlusive crises, ACS acute chest syndrome, AID autoimmune disease, SLE systemic lupus erythematosus, JIA juvenile idiopathic arthritis, AIH autoimmune hepatitis, M male, F female, ESR erythrocyte sedimentation rate, ANA antinuclear antibodies, RF rheumatoid factor

^afirst ascribed to SCD but probably related to JIA

Features arguing against SCD as the cause included bilateral symmetric pain limited to the joints, failure of hydroxyurea, persistent high erythrocyte sedimentation rate. In most previously reported cases, the recognition of SLE was delayed because of similar clinical features, regardless of involved organs [8–10]. The liver involvement is often misdiagnosed because jaundice is ascribed to hemolysis and not cholestasis.

An autoantibody production is traditionally a manifestation of autoimmunity. Nearly all our patients had detectable antinuclear antibodies. Whether early autoantibody detection might have helped to diagnose AID is discussed. The prevalence of antinuclear antibodies varies from 12 to 30% in healthy individuals overall [21, 22] and from 7 to 39% in Africans [23, 24]. Moreover, high autoantibody titers have been reported in SCD in the absence of autoimmunity [25, 26]. Consequently, routine screening for

autoantibodies in the absence of suggestive symptoms is not recommended, because it may be confusing and lead to inadequate diagnosis and therapy. The mechanisms underlying the production of autoantibodies in SCD are unknown but may involve impaired spleen function. Significant autoantibody titers have been found after splenectomy, in the absence of AID [27]. Other hypotheses include immune system overstimulation by multiple transfusions [28] and chronic inflammation [29]. This has not been confirmed in clinical studies [25, 26].

The treatment of coexisting AID and SCD is difficult [30]. Our patients experienced recurrent vaso-occlusive crises while on steroids [7, 10, 13, 30]. Concomitant red blood cell transfusion or exchange transfusion program may help prevent vaso-occlusive crises but increase the risk of anti-erythrocyte alloimmunization. Half of our patients received hydroxyurea in the first line or after chronic blood

Table 2 Treatment and last follow-up in the 8 patients

Patient	1	2	3	4	5	6	7	8
Treatment related to SCD before the diagnosis of AID	None	Hydroxyurea started at 13 y	Hydroxyurea started at 7 y	None	None	Hydroxyurea started at 9 y	Hydroxyurea started at 14 y	Chronic exchange transfusion programme started at 3 y splenectomy
AID	SLE	JIA	JIA	JIA	AIH	Sjogren's syndrome	SLE	AIH
Treatment of AID	NSAIDs Hydroxychloroquine	NSAIDs	NSAIDs for 3 years	Etanercept (No methotrexate because of chronic hepatitis B)	Steroids Chronic blood transfusions then Hydroxyurea ^a	NSAIDs (from age 11 to 13 y)	Steroids Chronic exchange transfusions ^a Hydroxychloroquine Aspirin	Steroids 6-mercaptopurine Chronic exchange transfusions ^a
2nd line	Genoidentical hematopoietic stem cell transplantation at 18 y	Etanercept	Steroids Intra-articular steroids	Azathioprine NSAIDs	Methotrexate Hydroxychloroquine Aspirin	Mycophenolate mofetil Steroids	Azathioprine Steroids	Chronic exchange transfusions ^a
3rd line and more			Etanercept for 5 years; (Failure of abatacept, infliximab, adalimumab) Current treatment: Tocilizumab + methotrexate			Mycophenolate mofetil		Liver transplantation at 10 y Ciclosporin and steroids
Last follow-up	CR	PR	Persistent activity	CR	CR	CR	PR	Normal liver function Controlled blood pressure

AID autoimmune disease, *SLE* systemic lupus erythematosus, *JIA* juvenile idiopathic arthritis, *AIH* autoimmune hepatitis, *NSAIDs* non steroidal antiinflammatory drugs, *CR* complete remission, *PR* partial remission

Patient 2: relapse after 3 years, then lost in transition to adult care, patient 7: persistent periventricular hyperintensity on cerebral MRI

^ain order to prevent occurrence of vasoocclusive crises

transfusion and experienced fewer vaso-occlusive crises. Hydroxyurea seems to be well tolerated by patients taking anti-inflammatory drugs [8–10]. TNF α antagonist therapy (etanercept) was promptly effective in our patients with JIA, as reported in patients with polyarticular onsets of JIA and no SCD [31, 32]. No severe etanercept-related complications were recorded. The few available data suggest good effectiveness and tolerance in patients with SCD [5, 20]. The use of others biological therapies as anti-interleukine 1 and 6 has not been reported yet in patients with SCD. Azathioprine was frequently used either for patients with SLE or autoimmune hepatitis and was well tolerated [10, 12–14]. For hydroxychloroquine, ocular toxicity may worsen retinopathy due to SCD and has to be regularly controlled. Finally, immunosuppressive and anti-inflammatory drugs can induce renal and hepatic toxicity that may be worsened by SCD-related complications. They may further increase the risk of infection [20], despite the lack of published data concerning infections in patients with both AID and SCD. The initiation of immunosuppressive and/or anti-inflammatory therapy should be discussed in reference centers and require close monitoring. Biological treatments, including anti-TNF targeted treatments, might be beneficial to SCD-associated AID / inflammation and in some cases to SCD itself and deserve further evaluation [33]. Hematopoietic stem cell transplantation seems to be a good therapeutic option. Liver transplantation can be discussed in very selected cases.

Conclusion

SCD and AID share many clinical and biological features, and diagnosing AID in patients with SCD can be challenging. Diagnostic delay increases the morbidity and mortality related to both the AID and SCD. Whilst the use of steroids to treat AIDs induced potential severe SCD-related complications, which justified associated chronic red blood cell transfusions, other treatments such as anti-TNF agents were well tolerated. Further studies are needed to determine the prevalence of AID in patients with SCD, to look for pathophysiological links, to earlier diagnose AID, and to define the best therapeutic options.

Abbreviations

ACS: Acute chest syndrome; AID: Autoimmune disease; AIH: Autoimmune hepatitis; CNIL: Commission Nationale Informatique et Libertés; JIA: Juvenile idiopathic arthritis; SCD: sickle cell disease; SLE: Systemic lupus erythematosus; VOC: Vaso-occlusive crises

Acknowledgements

Not applicable.

Funding

The authors declare that they have no funding.

Availability of data and materials

Please contact authors for data requests.

Authors' contributions

VL and FU collected data and wrote the manuscript; MM, VB, FL, BB and PQ were involved in the clinical care of the patients and provided data for the study. MM, FL and PQ helped with data management, edited and reviewed the manuscript. All authors read and approved the manuscript.

Ethics approval and consent to participate

According to the French legislation, no ethics committee agreement was required for such a retrospective survey. Patients data were included in the CEMARA registry for rare diseases which is approved by the French "Commission Nationale Informatique et Liberté" (Landais P, et al. CEMARA an information system for rare diseases. *Stud Health Technol Inform* 2010;160:481–5).

Consent for publication

Consent to publish was obtained from the parents or legal guardian, when they agreed to be registered in the CEMARA database.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

¹Onco-Hématologie Pédiatrique, Centre Hospitalier Universitaire Amiens, Amiens, France. ²Unité d'Immunologie-Hématologie et Rhumatologie Pédiatrique, Centre de référence pour la Rhumatologie et les maladies Auto-immunes Systémiques de l'Enfant, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Paris, France. ³Université Paris-Descartes, Paris, France. ⁴IMAGINE Institute, Paris, France. ⁵Hépatologie-Gastroentérologie-Nutrition Pédiatrique, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Paris, France. ⁶Pédiatrie Générale, Centre de Référence des Hémodémodinopathies, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris Labex-GR-Ex, Paris, France.

Received: 24 June 2017 Accepted: 26 December 2017

Published online: 17 January 2018

References

- Johnston RB Jr, Newman SL, Struth AG. An abnormality of the alternate pathway of complement activation in sickle-cell disease. *N Engl J Med*. 1973;288:803–8.
- Wilson WA, Nicholson GD, Hughes GR, Amin S, Alleyne G, Serjeant GR. Systemic lupus erythematosus and sickle-cell anaemia. *Br Med J*. 1976;1:813.
- Koethe SM, Casper JT, Rodey GE. Alternative complement pathway activity in sera from patients with sickle cell disease. *Clin Exp Immunol*. 1976;23:56–60.
- Wilson WA, De Ceulaer K, Morgan AG. Sickle cell anemia, complement, and systemic lupus erythematosus. *Arthritis Rheum*. 1979;22:803.
- Adelowo O, Edunjobi AS. Juvenile idiopathic arthritis coexisting with sickle cell disease: two case reports. *BMJ*. 2011; doi: <https://doi.org/10.1136/bcr.2011.4889>.
- Eberhard BA. Coexistent sickle cell disease and juvenile rheumatoid arthritis: 2 cases with delayed diagnosis and severe destructive arthropathy. *J Rheumatol*. 2002;29:1802. author reply 1802–3
- Nistala K, Murray KJ. Co-existent sickle cell disease and juvenile rheumatoid arthritis. Two cases with delayed diagnosis and severe destructive arthropathy. *J Rheumatol*. 2001;28:2125–8.
- Appenzeller S, Fattori A, Saad ST, Costallat LT. Systemic lupus erythematosus in patients with sickle cell disease. *Clin Rheumatol*. 2008;27:359–64.
- Khalidi NA, Ajmani H, Varga J. Coexisting systemic lupus erythematosus and sickle cell disease: a diagnostic and therapeutic challenge. *J Clin Rheumatol*. 2005;11:86–92.
- Saxena VR, Mina R, Moallem HJ, Rao SP, Miller ST. Systemic lupus erythematosus in children with sickle cell disease. *J Pediatr Hematol Oncol*. 2003;25:668–71.
- Maamar M, Tazi-Mezalek Z, Harmouche H, Mounfaloti W, Adnaoui M, Aouni M. Systemic lupus erythematosus associated with sickle-cell disease: a case report and literature review. *J Med Case Rep*. 2012;6:366.

12. Chuang E, Ruchelli E, Mulberg AE. Autoimmune liver disease and sickle cell anemia in children: a report of three cases. *J Pediatr Hematol Oncol.* 1997;19:159–62.
13. Lykavieris P, Benichou JJ, Benkerrou M, Feriot JP, Bernard O, Debray D. Autoimmune liver disease in three children with sickle cell disease. *J Pediatr Gastroenterol Nutr.* 2006;42:104–8.
14. El Younis CM, Min AD, Fiel MI, Klion FM, Thung SN, Faire B, Miller CM, Bodenheimer HC Jr. Autoimmune hepatitis in a patient with sickle cell disease. *Am J Gastroenterol.* 1996;91:1016–8.
15. Landais P, Messiaen C, Rath A, Le Mignot L, Dufour E, Ben Said M, Jais JP, Toubiana L, Baujat G, Bourdon-Lanoy E, Gérard-Blanluet M, Bodemer C, Salomon R, Aymé S, Le Merrer M, Verloes A, CEMARA task force. CEMARA an information system for rare diseases. *Stud Health Technol Inform.* 2010;160:481–5.
16. Hopkinson ND, Doherty M, Powell RJ. Clinical features and race-specific incidence/prevalence rates of systemic lupus erythematosus in a geographically complete cohort of patients. *Ann Rheum Dis.* 1994;53:675–80.
17. Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R, Silverman ED. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. *Arthritis Rheum.* 2007;56:1974–84.
18. Haffeejee IE, Raga J, Coovadia HM. Juvenile chronic arthritis in black and Indian south African children. *S Afr Med J.* 1984;65:510–4.
19. Vaiopoulos G, Konstantopolous K, Osterland CK. Asplenia in systemic lupus erythematosus: a simple coincidence? *Clin Exp Rheumatol.* 1995;13:513–5.
20. Michel M, Habibi A, Godeau B, Bachir D, Lahary A, Galacteros F, Fifi-Mah A, Arfi S. Characteristics and outcome of connective tissue diseases in patients with sickle-cell disease: report of 30 cases. *Semin Arthritis Rheum.* 2008;38:228–40.
21. de Vlam K, De Keyser F, Verbruggen G, Vandenbossche M, Vanneuville B, D'Haese D, Veys EM. Detection and identification of antinuclear autoantibodies in the serum of normal blood donors. *Clin Exp Rheumatol.* 1993;11:393–7.
22. Hilário MO, Len CA, Roja SC, Terreri MT, Almeida G, Andrade LE. Frequency of antinuclear antibodies in healthy children and adolescents. *Clin Pediatr.* 2004;43:637–42.
23. Adebajo AO, Charles P, Maini RN, Hazleman BL. Autoantibodies in malaria, tuberculosis and hepatitis B in a west African population. *Clin Exp Immunol.* 1993;92:73–6.
24. Greenwood BM, Herrick EM, Holborow EJ. Speckled antinuclear factor in African sera. *Clin Exp Immunol.* 1970;7:75–83.
25. Baethge BA, Bordelon TR, Mills GM, Bowen LM, Wolf RE, Bairnsfather L. Antinuclear antibodies in sickle cell disease. *Acta Haematol.* 1990;84:186–9.
26. Toly-Ndour C, Rouquette AM, Obadia S, M'bappe P, Lionnet F, Hagege I, Boussa-Khettab F, Tshilolo L, Giro R. High titers of autoantibodies in patients with sickle cell disease. *J Rheumatol.* 2011;38:302–9.
27. Balsalobre B, Hernández-Godoy J, Planelles D. Autoantibodies in splenectomized patients as a consequence of abdominal trauma. *J Investig Allergol Clin Immunol.* 1992;2:91–5.
28. Aygun B, Padmanabhan S, Paley C, Chandrasekaran V. Clinical significance of RBC alloantibodies and autoantibodies in sickle cell patients who received transfusions. *Transfusion.* 2002;42:37–43.
29. Allen RC, Dewez P, Stuart L, Gatenby PA, Sturgess A. Antinuclear antibodies using HEp-2 cells in normal children and in children with common infections. *J Paediatr Child Health.* 1991;27:39–42.
30. Couillard S, Benkerrou M, Giro R, Brousse V, Ferster A, Bader-Meunier B. Steroid treatment in children with sickle-cell disease. *Haematologica.* 2007;92:425–6.
31. Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, Sibilia J, Koné-Paut I, Gandon-Laloum S, LeBideau M, Bader-Meunier B, Mouy R, Debré M, Landais P, Prieur AM. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. *Arthritis Rheum.* 2003;48:1093–101.
32. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, Hospach T, Huppertz HI, Keitzer R, Küster RM, Michels H, Moebius D, Rogalski B, Thon A, Paediatric Rheumatology Collaborative Group. The German etanercept registry for treatment of juvenile idiopathic arthritis. *Ann Rheum Dis.* 2004;63:1638–44.
33. Solovey A, Somani A, Chen C, et al. Interference with TNF α using long-term etanercept in S⁺S^{Antilles} sickle transgenic mice ameliorates abnormal endothelial activation, vasoocclusion, and pulmonary hypertension including its pulmonary arterial wall remodeling. *Blood.* 2013;122:728.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at
www.biomedcentral.com/submit

