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Clinical and therapeutic aspects of sickle cell disease in three clinical cases

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One of the reasons of high pediatric mortality in developing countries, sickle cell disease is gradually emerging and is becoming a public health problem in many countries where it is rife. In Algeria the incidence is 2.7%. The management of sickle cell disease is increasingly better codified now thanks to better knowledge of the condition. It takes into account not only currently accepted universal principles but also the realities specific to our country.

Purpose: to share with health care professionals our therapeutic attitude during main acute complications as well as during the inter-critical phase of sickle cell disease in Algerian children.

Clinical cases. In this article, we presented three clinical cases concerning two adolescents and a two-year-old infant, carriers of major sickle cell syndrome, who were hospitalized for severe forms.

Conclusions. Providing right care for children with sickle cell disease could help prevent or improve many complications associated with this disease and allow them to lead healthier and more productive lives. Our patients were presented late. These cases revealed the problematic nature of early diagnosis, regular follow-up and early detection of complications in SCD patients especially with asymptomatic osteonecrosis of the femoral head.

The research was carried out in accordance with the principles of the Helsinki declaration. The informed consent of the patients was obtained for conducting the studies.

No conflict of interest was declared by the author.

Keywords: sickle cell disease, acute anemia, stroke, osteonecrosis.

Клініко-терапевтичні аспекти серпоподібноклітинної анемії у трьох клінічних випадках

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Однією з хвороб, що призводить до високої смертності серед дітей у країнах, що розвиваються, є серпоподібноклітинна анемія, яка поступово набирає поширення і стає однією з проблем громадської охорони здоров'я в багатьох країнах. В Алжирі захворюваність становить 2,7%. Ведення пацієнтів з серпоподібноклітинною анемією тепер набагато краще систематизоване завдяки більш глибокому розумінню цього стану. Воно бере до уваги прийняті нині універсальні принципи, а також реалії, характерні для нашої країни.

Мета — поділитися з медичними працівниками терапевтичною позицією під час основних гострих ускладнень, а також під час міжкритичної фази серпоподібноклітинної анемії серед алжирських дітей.

Клінічні випадки. У цій статті наведено три клінічні випадки у двох підлітків та дворічної дитини, що страждають на серпоподібноклітинний синдром, і госпіталізовані з приводу тяжких форм захворювання.

Висновки. Надання належного догляду за дітьми з серпоподібноклітинною анемією може допомогти запобігти або полегшити перебіг багатьох ускладнень, пов'язаних з цим захворюванням, та може дозволити їм вести здоровіше та продуктивніше життя. Пацієнти, описані в статті, були госпіталізовані пізно. Ці випадки виявили проблеми ранньої діагностики, диспансерного спостереження та раннього виявлення ускладнень у хворих на серпоподібноклітинну анемію, особливо у випадку безсимптомного остеонекрозу головки стегнової кістки.

Дослідження проводилося відповідно до принципів Гельсінської декларації. На проведення досліджень отримано інформовану згоду батьків, пацієнтів.

Автор заявляє про відсутність конфлікту інтересів.

Ключові слова: серповидноклітинна анемія, гостра анемія, інсульт, остеонекроз.

Клинико-терапевтические аспекты серповидноклеточной анемии в трех клинических случаях

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Одним из заболеваний, приводящих к высокой смертности среди детей в развивающихся странах, является серповидноклеточная анемия, которая постепенно распространяется и становится одной из проблем общественного здравоохранения во многих странах. В Алжире заболеваемость составляет 2,7%. Ведение пациентов с серповидноклеточной анемией теперь намного лучше систематизировано благодаря более глубокому пониманию этого состояния. Оно принимает во внимание принятые ныне универсальные принципы, а также реалии, характерные для нашей страны.

Цель — поделиться с медицинскими работниками нашей терапевтической позицией во время основных острых осложнений, а также во время межкритической фазы серповидноклеточной анемии среди алжирских детей.

Клинические случаи. Представлены три клинических случая у двоих подростков и двухлетнего ребенка, страдающих серповидноклеточным синдром, госпитализированных по поводу тяжелых форм заболевания.

Выводы. Оказание надлежащего ухода за детьми с серповидноклеточной анемией может помочь предупредить или облегчить течение многих осложнений, связанных с этим заболеванием, и может позволить им вести более здоровую жизнь. Пациенты, описанные в статье, поступили поздно. Эти случаи выявили проблемы ранней диагностики, диспансерного наблюдения и раннего выявления осложнений у больных с серповидноклеточной анемией, особенно в случае бессимптомного остеонекроза головки бедренной кости.

Исследование выполнено в соответствии с принципами Хельсинкской декларации. На проведение исследований получено информированное согласие родителей, пациентов.

Автор заявляет об отсутствии конфликта интересов.

Ключевые слова: серповидноклеточная анемия, острая анемия, инсульт, остеонекроз.

Introduction

About 2% of newborn babies suffer from sickle cell disease (SCD), predominantly Hb SS and SC disease types [3]. SCD has a worldwide distribution. It is estimated that 300,000 infants are born annually with SCD, most of them in sub-Saharan Africa [25,39]. Sickle cell disease is spreading around the world due to increased migratory flows and geographic spread of certain pathological genes. In some African countries, from 50 to 80% of children die before the age of five years [6,23]. Currently the SCD incidence in Algeria is 2.7% [8].

Pain (acute or chronic) is the hallmark feature of SCD [13]. The frequency and severity of painful episodes vary widely both across patients and over time in each patient. Effective treatment of acute pain is one of the most common and challenging problems in the management of SCD. Vaso-occlusion episodes (VOEs) are severe, which manifest themselves with acute pain as a result of VOEs with inflammatory and ischaemic consequences [34]. Other defined sickle cell disease complications include sequestration crisis (pooling the blood into an organ), aplastic crisis (reduced function of bone marrow), haemolytic crisis (rapid breakdown of blood cells causing a decrease in haemoglobin levels), acute chest syndrome (ACS), or other acute organ damage (including myocardial infarction), and stroke [13,16].

Immune function in pediatric SCD patients is impaired for variety of reasons, including deficient splenic clearance of opsonized encapsulated bacteria [10,11]. This results in a propensity to infection by encapsulated bacteria such as Streptococcus pneumoniae, *Haemophilus influenzae, Salmonella* typhi and non-typhi, and *Meningococcal species.*

Management includes treatment of the underlying infection, blood transfusion and some supportive measures. Hypersplenism may warrant elective splenectomy, though a more common presentation is functional hyposplenism as a result of splenic infarction. Acute painful crises may occur caused by a combination of VOEs and inflammation due to raising the intramedullary pressure. Small bones of the hands and feet as well as juxta-articular long bones may be affected. Painful crises can be precipitated by cold, infection, hypoxia, dehydration, stress [9].

Given the risk of poor adherence to daily prophylaxis and the development of penicillin resistant *Streptococcus pneumoniae* strains, immunization against pneumococcal infection as well as penicillin prophylactics is recommended. The recommended immunization schedule for previously unvaccinated children with SCD consists of three doses of conjugated vaccine 6 to 8 weeks apart, followed by a booster dose 1 year later, then by a polysaccharide vaccine after age of 2 years, with additional doses every 3–5 years [18].

The research was carried out in accordance with the principles of the Helsinki declaration. The informed consent of the patients was obtained for conducting the studies.

Clinical cases

During the follow-up of our patients with major sickle cell syndrome, we were confronted with extremely serious and rare clinical forms. The research was carried out in accordance with the principles of the Helsinki declaration. The informed consent of the patients was obtained for conducting the studies.

The **first patient** was a two-year-old infant with S/B thalassemia, who was consulted in the emergency unit for severe acute anemia. Clinical examination revealed intense skin and mucous pallor, pain in the region of spleen, tachycardia with the heart rate 130/min, and type III splenomegaly.

The **second patient was** a 13-year-old teenager, who referred to our hospital for the management of excruciatingly rebellious headaches with convulsive illness. Post critical clinical examina-

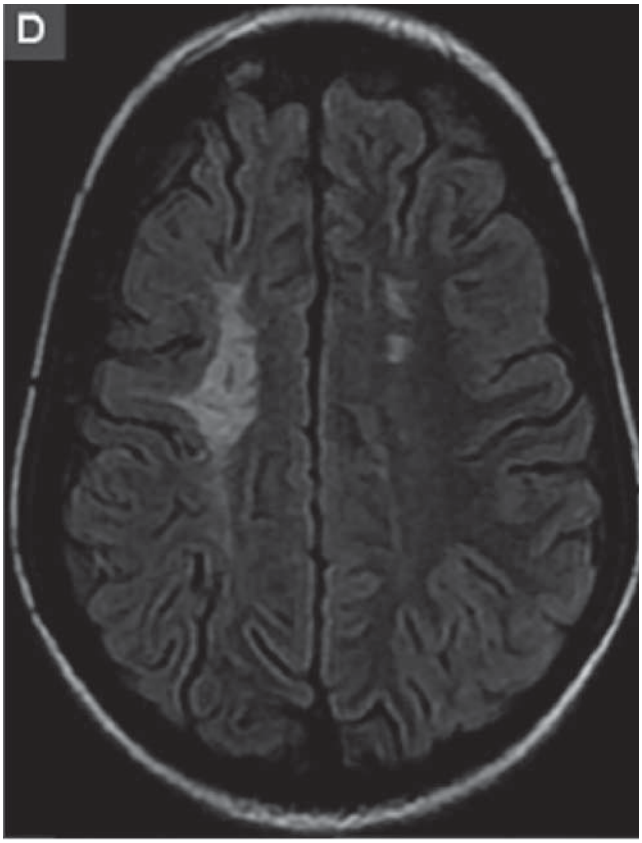

Fig. 1. Axial view, bilateral lesions of the anterior junctional white matter, extended in the right range, multiple hypersignals on the left

tion found the adolescent girl in stage I coma, afebrile, hemodynamically stable with moderate skin-mucous pallor, with no fever. Her weight was 27.4 kg and height 139 cm with a body mass index of 14.18 kg/m^2. The arterial pressure was 110/60 mm Hg,:the heart rate was 112 beats/min; the respiratory rate was 32 per minute. Hemiparesis of the right half of the body was revealed.

The **third patient**, a 12-year-old teenager, who was admitted in emergency for lameness. On clinical examination, there was pain on palpation of the right lower limb, with limited abduction movements of the same limb. Furthermore, he was afebrile but reported a pain score of 3 according to the Visual Analogue Scale (VAS).

Results

For our little infant, the blood count found an acute anemia at 4 g/dl, the reticulocyte rate was 400,000/mm^3. Our emergency management quickly corrected this acute anemia by blood transfusion after a bedside compatibility test, increasing the hemoglobin level to a baseline hemoglobin of 9 g/dl. The transfusion took two hours and a half, due to the low hemoglobin level on admission. For the adolescent admitted in convulsive state, magnetic resonance imaging showed the absence of aneurysm or arteriovenous malformation (Fig. 1,2).

The teenager of the second clinical case had benefited from hyperhydration with analgesics. Then a transfusion exchange was performed aimed at reducing hemoglobin S to 30%. Currently the teenager is on a transfusion exchange sub-program with rehabilitation sessions for her right hemiplegia. For other 12-year-old boy, the hip x-ray revealed radiological abnormalities. Magnetic resonance imaging of the hip had found foci of dif-

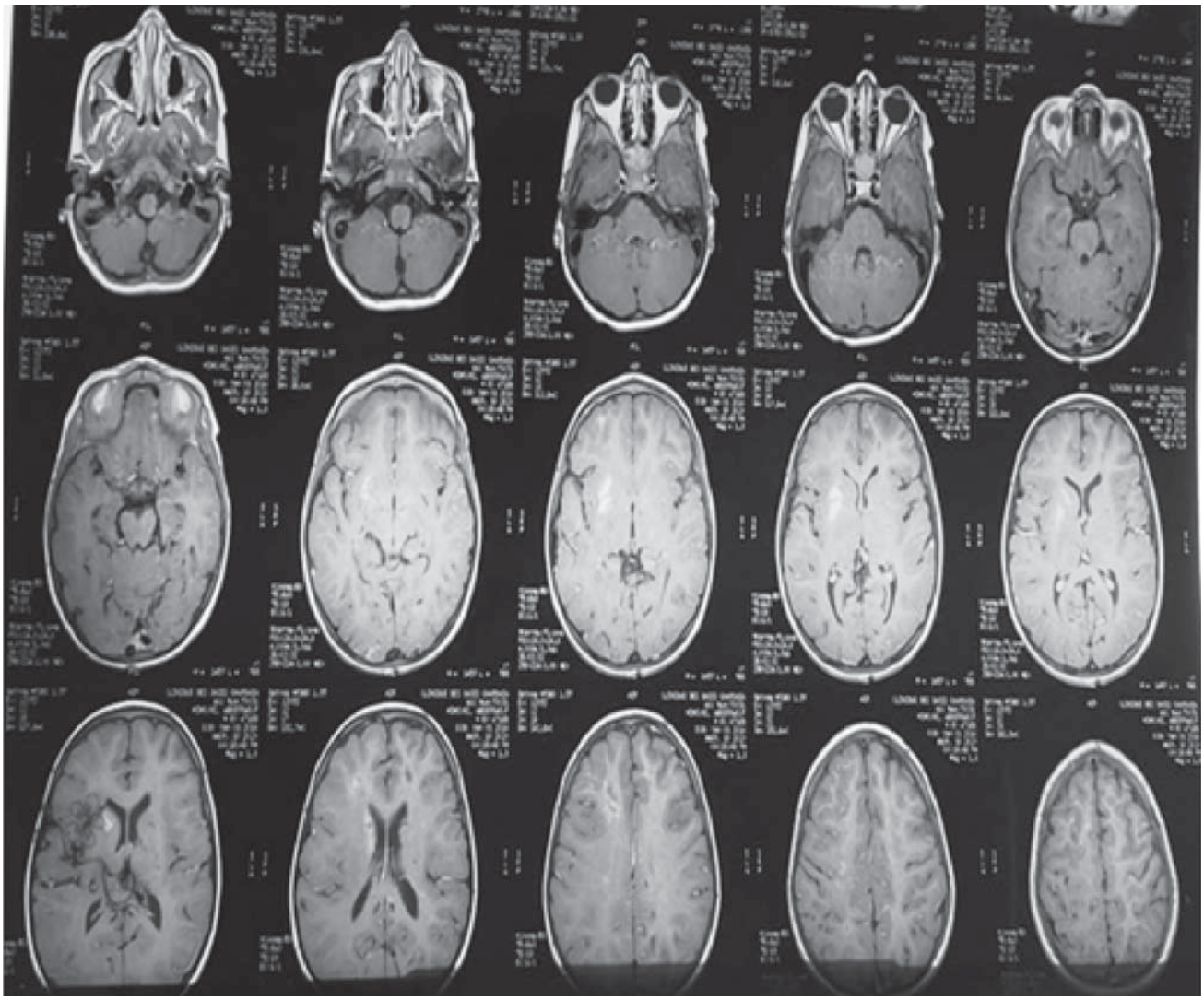

Fig. 2. Early subacute ischemics of the corona radiata of the right fronto-parietal junctional zone, late subacute ischemical lesion of the left deep white matter, multiple micronodular lesions of the deep white matter and periventricular more important diffuse at the level of the right hemisphere

fuse upper left femoral epiphyseal bone infarction, left upper metaphyseal, and focal right upper femoral epiphyseal (Fig. 3).

The teenager benefited from hyperhydration with analgesics for level 2. Orthopedic treatment was offered with a splint kept in abduction for six months with radiological controls. After a year of follow-up, he resumed walking with slight right lameness, and was put on the «Hydrea» because of the severe clinical course of his disease (an acute chest syndrome, several attacks of vasoocclusive crises).

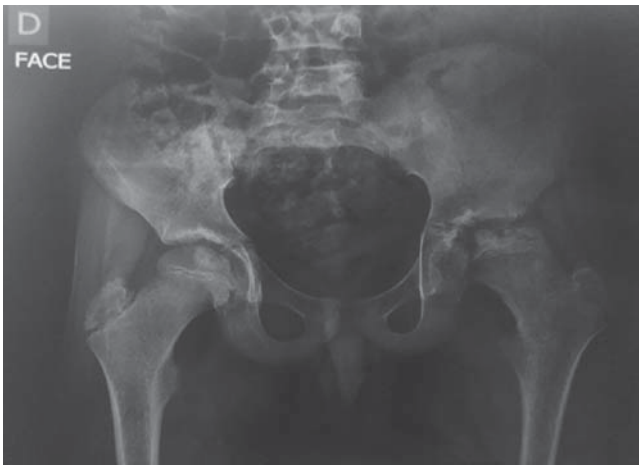

Fig. 3. Decrease in left and right epiphyseal height with irregular appearance of the left epiphyseal contours

Discussion

Since the average lifespan of sickle cells is about two weeks due to chronic hemolysis, there is very active erythropoiesis. Each patient has a baseline hemoglobin level which is specific to them and results from the hemolysis-production balance, this level generally varying between 6 and 11 g/dL and remaining more or less stable for the same patient in the absence of complications.

Acute splenic sequestration is defined as an increase in the size of the spleen of 2 cm, and a drop in hemoglobin of at least 2 g/dl, frequently accompanied by thrombocytopenia and general and abdominal signs [12].

Children with homozygous sickle cell disease (HbSS) are often affected until the age of six while individuals with other heterozygous forms of sickle cell disease (HbSβThal, HbSC, HbSD) are at risk even during adulthood [15]. In addition, most of the patients hospital courses were characterized by hemodynamic instability manifesting with hypotension, tachycardia, or orthostasis [27]. The incidence of Acute Splenic Sequestration Crisis (ASSC) was found to occur in 10 to 30% of SCD children younger than 5 years [17,21]. After the second episode, a transfusion program should be discussed for children. A splenectomy is sometimes justified in severe or recurrent forms. Education of parents on palpation of the spleen and recognition of signs of acute anemia is therefore essential [7]. Subsequent transfusions, if necessary, should be administered with caution and in smaller volumes due to the potential for autotransfusion of sequestered blood which could result in hyperviscosity. Splenectomy should be considered in cases of severe or recurrent acute splenic sequestration [11].

Our first patient has no indication for splenectomy since he has never had an identical episode.

Another serious complication in pediatric hematology is cerebral vasculopathy. Ischemic stroke is 250 times more common in children with sickle cell disease than in the general pediatric population.

Stroke symptoms and signs in SCD patients are similar to those in other stroke patients; therefore, excluding other traditional risk factors is mandatory. According to literature data, in children 27% of ischemic strokes are manifested by the first epileptic seizure [32]. Convulsions iare the revealing mode of the ischemical cerebral accident in our patient.

The prevention is done by the practice at the age of 12 months of the DTP with measurement of the cerebral wave fastness which must not exceed 20 mm/s. The management is twofold: primary prevention, i.e. prevention of the first stroke which affects the child, and prevention of recurrence (secondary prevention) after the first stroke. Primary prevention is based on two findings: the majority of cerebral infarctions are secondary to obstruction or occlusion of the internal carotid artery or anterior cerebral arteries; the need for screening for the risk of stroke by ultrasound examination and transcranial Doppler examination from the age of 12/18 months because of the negative correlation between circulatory speeds and the diameter of the arteries [37].

Compared with normal populations, individuals with SCT show increased coagulation activity measures with higher levels of D-dimers, thrombin-antithrombin complexes, and prothrombin fragments, and their absolute blood monocyte levels are higher [36]. Subclinical sickling occurs in these cases upon loss of normal phospholipid asymmetry, resulting in abnormal phosphatidylserine that contributes to hemostatic problems [5,33].

Therefore, in the setting of a focal neurological deficit, it is important not to miss the second com-

plication like aneurysms with or without subarachnoid hemorrhage while deciding on acute or secondary preventive strategies [4,29].

There is consensus in the literature that abnormal TCD (e.g. high-risk classification for stroke) in children indicates a chronic transfusion regimen to prevent the first episode, i.e. primary prevention using regular transfusion program (RTP) [1,2]. However, the use of RTP after an abnormal TCD eventually treats about 40% of children who would not progress to clinical stroke, exposing them to repeated transfusions, which are not risk-free [22]. If a child who had abnormal TCD screening measurement meets criteria for transitioning to maximum tolerated dose of hydroxyurea, after 1 year of regular blood transfusion therapy, a discussion with the family should include whether hydroxyurea is preferable to regular blood transfusion therapy [38]. Prior to consideration of transitioning from regular blood transfusion therapy to maximum tolerated dose of hydroxyurea, MRI of the brain should be completed to exclude silent cerebral ischemic lesions, and intracranial MRA should be completed to determine the presence and extent of cerebral vasculopathy, per the TWiTCH protocol [38].

The third complication that can be seen in major sickle cell syndromes, is aseptic osteonecrosis of the femoral head, with prevalence from 2.9% to 41% [24,28] and with incidence ranging from about 2 to 4.5 cases per 100 patient-years [26].

Studies have shown the relationship between the fetal hemoglobin rate and the incidence of morbid events in patients with sickle cell anemia, and found a significantly lower incidence of avascular necrosis (considering any location) when the HbF levels were above 10% [31]. 99mTc scintigraphy and MRI are useful for diagnosis. More recently, MRI has largely replaced radionuclide bone scintigraphy because of its greater sensitivity (up to 100%, compared to 90% for bone scintigraphy) [35]. Magnetic resonance imaging is the most sensitive and specific radiological modality in the detection of osteonecrosis [20,30]. MRI with diffusion sequences, T2 mapping and mapping of the apparent diffusion coefficient has also been advocated more recently, although the utility of these techniques for the assessment of osteonecrosis remains to be investigated [14,40].

The treatment is not codified. For femoral involvement, it must combine bed rest, analgesic treatment and possibly immobilization. In the pediatric population, treatment is based on the age of disease onset, associated symptoms and the extent of femoral head involvement. Treatment options range from non-operative symptomatic treatment for weight relief and cast with fixation on femoral and pelvic bones following surgical procedures.

Treatment options include early stage femoral head decompression, rotational osteotomies, and late stage prosthetic surgery, osteotomies. Early intervention has been shown to improve outcomes [19].

Conclusion

Providing the right care for children with sickle cell disease could help prevent or improve many complications associated with this disease and enable them to lead healthier and more productive lives. Our patients were presented late. These cases revealed the problematic nature of early diagnosis, regular follow-up and early detection of complications in SCD patients, especially with asymptomatic osteonecrosis of the femoral head.

No conflict of interest was declared by the author.

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