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Review Article

Spinal Manifestation of Sickle Cell Disease. A Report On 35 Patients with Literature Review

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Abstract:

Background: Sickle cell disease is a hereditary hemoglobinopathy affecting the spine in a wide range of pathology. Despite the several pathological involvements, some patients remain asymptomatic even with positive imaging findings.

Objectives: Theme of this study is to report the various pathological disorders involving the spine of patients with sickle cell disease in Basra "south of Iraq"

Patients and method: 35 Homozygous and heterozygous sickle cell patients were included in this study. 22 Males and 13 females, their age range from 6 to 69 years they were evaluated clinically, and also by laboratory imaging studies like plain radiography, computerized tomography, magnetic resonance imaging and mineral bone density "DEXA scan "

Results: 54% of the patients were homozygous, and the remaining were heterozygous, 66% of them were asymptomatic, back pain was the complaint in 60% while spine tenderness was reported in 40%, 31% had tenderness in the sacroiliac region and only 6% had neurological claudication and focal neurological deficit. Biconcave vertebra was confirmed in 72% of the patients and mainly localized in the lumbar Spine, MRI findings of vertebral infarction were observed in 58% of the studied patients while sacroiliac joint changes appeared in 60%, 60% of those who had DEXA scan showed low mineral bone density in the lumbar spine

Conclusion: Sickle cell disease involve the whole Spine in a wide range of pathological process, some show clinical symptoms, and some remain asymptomatic in spite of changes. The structural changes are more obvious in the homozygous group (55) the lumber spine is dominantly involved, disc prolapse, and neurological deficit is rare while the low mineral changes is common. We did not report a case of spondylodiscitis in this series, though it is very much expected, so routine screening of the spine in sticklers is mandatory

Introduction:

Sickle cell disease "SCD" is an inherited hemoglobinopathy caused by mutation in the six amino acid of the b globin gene HBB, this is one of the most common serious, genetic disease in children, and lead to significant morbidity and mortality especially in people of African and Mediterranean countries (Joseph, E Maakaron) (1).

Sickle cell disease was first described in 1910 in a dental student presented with pulmonary symptoms, Herrick (2) coined the term sickle shaped to describe the particular appearance of the RBC in this patient. However, at that time he was not sure that this abnormal blood condition was a disease itself or a manifestation of another disease.

Sickle cell disease is particularly common in many people who came from subSaharan Africa, India, Saudi Arabia, and Mediterranean countries.

In some area of sub-Saharan Africa, up to 20% of children are born with this condition (piel FB, et al.) (3).

The abnormal morphology of hemoglobin and sickle cell disease starkly reduce the flexibility of red cells so they become rigid sickle shaped in low oxygen tension, moreover, not able to resume the normal shape even after normalization of oxygen tension, so it cannot cross the capillary bed leading to subsequent vessel occlusion, which usually lead to ischemia and infarction (Rudy H et al)(4).

Physiological stress high attitude, temperature changes and dehydration, all can precipitate red cells sickling, which lead to crisis, which when become repetitive can lead to spinal pathology like infarction infection, or change in the vertebral shape (Rudy HL) (4).

Due to repetitive infarction and subsequent Marrow hyperplasia the bone becomes soft, resorbed with subsequent deformity, this probably is related to inflammatory cytokines such as tumor necrosis factor alpha, and interleukin 6 that are released in bone

during ischemic condition (Teitelbaum SI) (5).
Spine infection is a common pathology in sticklers. This is because of the effect of tissue infarction immuno deficiency secondary to splenic dysfunction and excess iron secondary to increase red cell turnover, which is a good bacterial nutrient. (Almeida A et al) (6).
Studies show that the most common pathogenesis of osteomyelitis are salmonella species and staphylococci species in some cases anaerobic microorganism like bacteroids E. coli have been reported (Ebony ww)(7).
Spinal involvement and sickle cell disease is very common and contribute to significant morbidity and mortality.
The acute problems include vaso-occlusive, painful crisis, spondylodiscitis and vertebral body compression fracture. The chronic problems are vertebral and Marrow infarction.
Reduction of the vertebral bone density and structural changes (Rudy HL,Almeida A et al) (4,6).
Vaso-occlusive crisis is common in sickle cell disease and virtually affects old patients, and often begins in late infancy and reoccurring throughout life (HUOMH ET AL) '8'.
The process can occur in any organ but common in bone marrow and results in infarction (lonergan GJ et al) (9).
Roughly 2/3 have involvement of the lumbosacral spine

Decreased bone density:

After birth, the red marrow undergoes a gradual conversion into yellow or fatty Marrow this in the normal person while in sickle cell patients, because of the rapid removal of the red blood cells by reticuloendothelial system that compensate with re-conversion of the yellow marrow, to red marrow with intramedullary hyperplasia this lead to widening of the medullary space and thinning of the cortices this lead to decrease bone density(Ejindu etal) (10).

Spinal canal diameter:

In a study done by (seraslane et al) (11). spinal canal diameter in patients with sickle cell disease was observed to be less than those healthy individuals, so they tend to be shorter and less in weight

Central nervous system infarction:

Occlusive vascular disease of the central nervous system is the most serious neurological complication in Sicklers leading to infarction.
Parenchymal lesions are most common in the brain, chiefly in the cerebral arterial boundaries zone, while spinal cord infarction is extremely rare. (12)

Sacroiliac involvement:

This joint is often involved to various degrees and it is a real source of pain.
Technically, it is confirmed by clinical test and imaging like CT scan (manzary m) '13' According to New York scoring criteria, SI joint changes can be graded as follow
Grade 0: no abnormality
Grade 1: suspicious changes (no specific abnormality)
Grade 2: minimal sacroiliitis (loss of definition of the age of the SI joints. There is some sclerosis and perhaps minimal erosion. There may be some joint space narrowing)
Grade 3: moderate sacroiliitis (definite sclerosis on both side of the joint blurring and in distinct margins erosive of changes with loss of joint space)
Grade 4: complete fusion and ankylosis of the SI joint (without any residual sclerosis) (dale K) '14' and (van tubergen etal) '15'
The aim of our study is to report spinal involvement in sickle cell disease with special emphases on the incidence of certain pathology and review of the related literatures.

Patients and methods:

This is descriptive, cross-sectional study was conducted in Basra Teaching Hospital from June 2019 to January 2021
This study included (35) patients with sickle cell hemoglobinopathy their age ranges from (6 to 69 years) with mean of 29.9 years. (22, males 13 females)

Inclusion criteria:

All age groups, homozygous sickle cell disease, heterozygous sickle cell disease Patients with previous trauma were excluded after signing the informed consent, according to the previously prepared questionnaire sheet history was taken, and clinical examination was performed with a special emphasis on the spine.
Laboratory investigations like Hb level CBC,HB variant, ESR CRP blood urea and and serum electrolytes were requested and evaluated. 35 patients were sent to plain radiography of the whole spine and pelvic radiography were requested and evaluated for 28 patients CT scan for 10 patients MRI for 24 patients and DEXA scan for 10 where requested Adult patients were assessed by CT and DEXA spine Pain was scored into mild pain. What could be ignored, moderate which could not be ignored and severe, which was present most of the time, demanding constant attention and/or treatment. Spinal canal diameter was measured in axial view and mid sagittal Statistical analysis of the data was analyzed using SPSS version 25 database

Results:

In the spinal clinical features 23 patients (66%) complained from back pain. While 12 patients (34%) where asymptomatic. The single case of neurological deficits presented with foot drop because of the spondylolisthesis

Table 1: shows the details of the clinical findings

Clinical findings	NO. of patients	% of patients
Back pain	23	66
Spine tendreness	14	40
Recurrent painful spinal crisis	12	34
SI joint tenderness	11	31
Neck pain	2	6
Lower limb radiculopathy	2	6
Neurological claudication	2	6
Focal neurological deficit	1	3

According to Pain scoring 13 patients complained from mild

pain, 7 patients had moderate pain and 3 patients presented with severe pain all those with severe pain were from homozygous a group.

Analysis of the HB electrophoresis revealed 54% were homozygotes 23% were sickle thalassemia while 23% were trait.

Table 2: shows the relationship between Hb electrophoresis, and the presence or the absence of symptoms

Clinical findings	HBSS NO.	HBSF NO.	HBSA NO.	Total NO
Symptomatic	11 (31%)	7 (20%)	5 (14.2%)	23 (65.7%)
Asymptomatic	8 (22.8%)	1 (2.8%)	3 (8.5%)	12 (34.2%)
Total	19 (54.2%)	8 (22.8%)	8 (22.8%)	33 (100%)

Strikingly in one patient the HB level was 16 g/L. This is because he was smoker and sickle cell trait and in one the ESR level was 120 mm/h. His condition was not good. He was suffering from concomitant chest infection and spinal vaso-occlusive crisis.

Table 3: result of general laboratory investigations

Laboratory investigations	Range	Mean
HB Level g/dl	6.1-16	9.7
WBC Count 10^3/ul	2.9-19.7	9.2
Reticulocyte count 10^6/ul	1.5-5.6	3.6
CRP in mg/dl	2-85	10.9
ESR	4-120	24.8
Blod urea in mg/dl	14-50	25.5
S.creatinine mg/dl	0.29-1.8	0.67

Table 4: show the radiological findings

Imaging findings	NO. of patients	% of patients	NO. of the observed
Biconcave vertebral body	23	72	32
Sacroiliac joint changes	17	60.7	28
Vertebral body infarction	14	58.3	24
H shaped vertebral body	8	25	32
Coarse trabeculation	8	80	10
Lumbar spine spondylotic changes	7	29.2	24
Cervical spine spondylotic changes	3	12.5	24
Tower vertebra	2	6.25	32
Lumbar disc prolapse	1	4.2	24
Lumbar spondylolisthesis	1	3.1	32

Total appearance of structural changes that include biconcave H shaped vertebra, and tower vertebrae were in 72% of the patients and these changes appeared in spine radiography, CT and MRI all Scan.

Sacroiliac joint changes were observed by pelvic radiographs, and CT scan also demonstrated in the enclosed figure

Spine MRI reveals spondylotic (enclosed figure)

The age of patients with lumber spondylosis ranged from 44 to 69 years while those with cervical spondylosis their age ranged between 38 to 69 years MRI showed vertebral infarction and 14 patients 8 symptomatic and 6 asymptomatic (enclosed figure) for the detection of coarse trabeculations we depended on CT scan (Enclosed figure)

There was no case of cervical spine, disc prolapse; spondylodiscitis is reported in the MRI

The association between biconcave vertebra and recurrent attack of spinal crisis is more with biconcave vertebra

Table 5: show the above correlation

Structural changes	NO.of patients with recurrent crisis	% of patients with recurrent crisis	NO. of patients without crisis	% of patients without crisis	Total
Biconcave vertebra	10	87.5%	1	12.5%	8
H shaped vertebra	2	43%	13	57%	23

The distribution of the presence of biconcave, H shape and tower vertebra that were observed in the imaging of 32 patients and their relationship to the HB variants of the patient showed below in table 6.72% of the patients had radiological findings.

Table 6 show the correlation between the presence of vertebral body structural changes and HB variant

Structural changes	HBSS	HBSF	HBAS	Total NO & %
Presence of changes	14 (43.7%)	6 (18.7%)	3 (9.3%)	23 (71.8%)
Absence of changes	4 (12.5%)	1 (3.1%)	4 (12.5%)	9 (28.1%)
Total No.	18 (56.2%)	7 (21.8%)	7 (21.8%)	32 (100%)

The appearance of vertebral body infarction has appeared in the MRI of 24 patients and its distribution is related to sickle-cell variant is shown in table No. 7. about 58% of patients showed signs of infarction versus 46.6% did not show these changes.

In the positive cases of infaction 71% were of the homozygous variant while 29% were of the heterozygous and 8 patients (33%) where symptomatic while 6 patients (25%) were asymptomatic

Infarction status	HBSS No. & %	HBSF No. & %	HBAS No. % %	Total No. & %
Presence of infarction	10 (41.6%)	3 (12.5%)	1 (4.1%)	14 (58.3%)
Absence of infarction	4 (16.6%)	3 (12.5%)	3 (12.5%)	10 (46.6%)
Total No.	14 (58.3%)	6 (25%)	4 (16.6%)	24 (100%)

Sacroiliac joint changes may be unilateral or bilateral. These changes were noticed in pelvic photography and/or CT scan, which may include joint space narrowing or widening, surface erosion, subchondral sclerosis, and partial or complete ankylosis.

Table 8 below show the changes

Sacroiliac joint changes	No. of patients	% of patients
Bilateral involvement	4	23.5
Unilateral involvement	13	76.5
Total No.	17	100

Spinal canal diameter was evaluated by CT scan The result is summarized in table 9. mean of cervical canal diameter was 14.8 mm, for the thoracic spine was 14.2 mm and for the lumbar spine was 14.8 mm

Table 9 show the result of spinal canal diameter

Segment of the spine	Range in mm	Mean in mm
Cervical spine	11.5-17.2	14.8
Thoracic spine	11.5-16.5	14.2
Lumbar spine	12.5-18.5	14.8

Spinal bone density was evaluated by DEXA scan for 10 patients, their age ranged from 18 to 39 years and the results of T score is shown below in table, 10 , All patients with low bone density were homozygous, and all those with normal Bone density were heterozygous

Table 10 bone mineral density measurements

DEXA T score	No. of patients	% of patients	Mean HB level mg/dl
Normal	4	40	11.5
Osteopenia	4	40	8.6
osteoporosis	2	20	8.4

The distribution of structural changes and vertebral body abnormalities according to each segment of the spine involved as shown below in table 11

The involved spinal structural abnormality	No&% of patients with abnormality in lumbar spine	No&% of patients with abnormality in dorsal spine	No&% of patients with abnormality in cervical spine	Total no. of patients observed for abnormality
Biconcave vertebra	23 (72%)	16 (50%)	5 (16%)	32
H shaped vertebra	8 (25%)	4 (12.5%)	0	32
Tower vertebra	1 (3%)	1 (3%)	0	32
Vertebral infarction	12 (50%)	10 (42%)	6 (25%)	24
Coarse trabeculation	8 (80%)	7 (70%)	2 (20%)	10

Discussion

in our study, we found that 23 patients with sickle cell disease where symptomatic in a percentage of 60% while the remainder 12 patients 34%, asymptomatic, 3 patients 9% presented with acute severe back pain while 20 patients complained from mild to moderate pain for longer period. These findings cannot be compared with a study done in 1994, by sadat-Ali etal (16) In which 23 patients (68%) presented with acute severe back pain and 11 patients (32%) had chronic pain Study in ornan(Knox-macaulay etal)(17) revealed that 50% of heterozygous patients were asymptomatic while in our current research only 11% were asymptomatic and another study by Jean baptiste,etal(18) in 2000 only 6 patients were asymptomatic, and their MRI showed signs of infarction while in our study, 14 patients, (58%) their MRI revealed infarction with only eight patients (33%) were symptomatic and six patients (25%) where asymptomatic

Both, Keely k etal(19) and Roger E etal(20) mention the back pain is related to vaso-occlusive crisis not infarction. They were admitted to the hospital and discharged home2 to 3 days.

Moreover, Keely K etal(19) confirmed that back pain is 50 times more likely related to vaso-occlusive than due to infarction. All these patients were of homozygous group, which is worse than the heterozygous. This suggestion is in agreement with Golding. Etal(21) who stated that the vaso-occlusive crisis is less common in heterozygous variants

Roger E etal(20) mentioned that in 71% of the patients local tenderness over the spinous process was confirmed. This is not an agreement with our study in which were found only 40% with tenderness over the spinous process

Vertebral structural changes in form of biconcave vertebra in most series was 22 (40%) in older patients. Digg SL etal (27) ,Sadat-Ali etal (16) found that these changes occur in 44% of his patients while Golding etal(21) noticed these changes in 70% of his patients but we found this changes in 72% of our patients, so our percentage is higher than the recorded in the literature

Marlow etal(23) in their study of 56 patients with thoracic and lumbar vertebra, spinal radiography observed at 17 (44%) patients showed biconcave fish vertebra, and, 31(81%) showed H vertebra and, 8 (14%) showed evidence of tower vertebra deformity, in comparison to our study, we confirmed, and we found the appearance of biconcave vertebra in 23 Patients(72%) H shaped vertebra in 8 patients(25%) and tower vertebra in 2 Patients(7%)

LeongGS etal(24) demonstrated the appearance of H shaped vertebra in approximately 10% of Patients but it is essentially pathognomonic for sickle cell disease

Roger etal (20) in their study, demonstrated that the segment of vertebral column in which biconcave vertebra appeared, were in lumbosacral, in 66% of the cases, followed by the thoracic in 22% and cervical in only 12%, we record the different percentages in our study, where 72% in lumbar region, 50% in thoracic and 15.5% in cervical spine.

Bahebeck etal(25) describe the presence of infarcts in the lumber Spine of 20 patients (40%) from the total of 84 patients in his series.

We also found the involvement of the lumbar vertebra is more than the thoracic or cervical vertebra. Also the MRI findings of infarction in our series was only in 14 patients which comes to

58% of those who had MRI study

HUOMH etal (8) mentioned that the severity and frequency of structural changes and infarcts are generally less in sickle thalassemia, due to higher levels of normal heamoglobin molecules in those patients, patients with heterozygous sickle cell trait, usually have sufficient amount of heamoglobin to preclude hypoxic episodes under physiological conditions

This result agrees with our which showed only six sickle thalassemia patients had structural changes in contrast to 14 homozygous patients from a total of 32 patients Observed Also, in our study, only three patients with sickle thalassemia revealed sign of infarction in the MRI while 10 Patients of the homozygous group show that abnormality from total number of 24 patients observed for infarction. In our study of 35 Patients we did not record a single case of spinal infection Desouza(26) found that osteomyelitis of the spine is a rare condition with an incidence of 0.45% of all cases of osteomyelitis Roger etal(20) noticed that no infectious process were found in their study, this result is identical to ours. The same report by skaggs et(27) and their study recorded no case of spondylodiscitis, all the above studies and ours, reinforce the rarity of spondylodiscitis in sicklers, in contrast sadat-Ali etal(16) in 1994, recorded eight Patients(24%) in his study involved with infective spondylitis In our series, only one patient had a small non-significant lumbar disc confirmed by MRI. We did not come across research about disc prolapse in sicklers.

We feel probably the reason because of less activity, and weight in sicklers or structural vertebral malformation lead to central bulge toward the vertebral end plate rather than the neural foramen We performed evaluation of the spinal canal diameter by CT for 10 adult patients. Our results showed that the canal diameter in the cervical spine was 14.8 mm, for thoracic spine was 14.2 mm and for lumber spine was 14.8 mm.

Our findings are considered near normal according to the study by Talekar etal (28) in 2017, but our result is not in agreement with the result of serarslan etal(11) 2010, who stated that spinal canal, diameter, in Patients with sickle cell disease was observed to be less than that of healthy individuals as they tend to be shorter and weight less

We evaluated the spinal bone mineral density by DEXA scan for 10 patients and found that 40% of the tested patients had normal bone mineral density, 40% were osteopenic and 20% osteoporotic all patients with low mineral density, homozygous, and all the normal results were heterozygous.

Our Study is not in agreement with the study of Baldazi G etal he studied 65 sicklers their age over 20. They found 12 patients (18%) had normal bone mineral density, 37 Patients (57%) had osteopenia, 16 patients (25%) head osteoporosis, among the 60 HBSS Patients 10(16.5%) had normal bone mass density, 34(57%) had osteopenia and, 16(20.5%.) had osteoporosis, while among the five HBFF patients two had normal BMD and three had osteopenia.

Another study done by Sarrau etal(30) 2007, in which they took 103 sicklers 15 years and older and found that 63% of sickle patients who had low bone mass density were homozygous while, 61% of those with normal bone mass density were heterozygous.

Chronic severe anaemia, lead to burden on bone marrow with increase erythropoiesis leading to hyperplasia of bone marrow, a decrease in trabecular network and osteopenia (brinker etal (31)) And bone destruction(voskaridoe etal(32))

Some studies by Brinker etal (31) and Miller RG etal(33) did not find any correlation between HB level and bone mineral density values while in our study, we found that the mean HB level in osteoporosis was 8.4 mg/dL in osteopenic mean was 8.6 mg/dL and in patients with normal bone density It was 11.5 mg/dL.

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