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The Nervous System in Sickle Cell Disease

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Summary. The various neurological manifestations encountered in thirty-three Nigerians out of a total of 257 with homozygous (SS) sickle cell disease were described. These included mental changes, disturbance of consciousness, convulsions, meningism, cranial nerve palsies, cerebrovascular accidents and paraparesis. The high incidence of meningitis, particularly pneumococcal meningitis, was noted. Intracranial haemorrhage and dural sinus thrombosis carried poor prognosis. Cerebral angiography demonstrated occlusion of a major cerebral artery in one case, and pneumoencephalography showed internal hydrocephalus in two other cases. The literature on the involvement of the nervous system in sickle cell disease was briefly reviewed.

Résumé. Des manifestations neurologiques variées ont été observées dans trente-trois cas sur 257 drépanocytoses homozygotes (SS) au Nigéria. Il s'agit de troubles du comportement ou de la conscience, de convulsions, de méningisme, de paralysies des paires craniennes, d'accidents vasculaires cérébraux, ou de paraparésie. L'existence de méningite; a pneumocoque en particuliers a été observée. Une hémorragie intracranienne, ou une thrombose, d'un sinus sont de fâcheux pronostic. L'artèriographie carotidiene met en évidence une obstruction d'une grosse artère cérébrale dans un cas, et l'encéphalographie gazeuse montre une hydrocéphalie dans deux autres cas. Les auteurs font une brève revue de la littérature des manifestations neurologiques dans le drépanocytose.

INTRODUCTION

Sickle cell disease is probably an old affliction of man (Konotey-Ahulu, 1968a), but its recognition as a clinical entity is relatively new (Herrick, 1910; Ferguson, Carrington & Scott, 1955). Dresbach (1904) reported 'peculiar anomaly in the red blood cells' in a 22-year-old Mulatto in Ohio who had rheumatic symptoms but died before a conclusive diagnosis was made. Sergent & Sergent (1905) examined the blood of many natives of Algiers and found that about 5% of them had 'demilune' red blood cells which they attributed to malaria. However, Herrick (1910) is universally credited with the first authentic account of

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sickle cell disease as a clinical entity. He described a 20-year-old Negro from Grenada, West Indies, with severe anaemia who had 'peculiar elongated and sickle shaped red blood cells'. Soon the protean manifestations characteristic of the disease were recognized, one of the basic causes of which is a vascular occlusive phenomenon which may affect any system/systems of the body (Margolis, 1951; Ferguson *et al.*, 1955; Mabayoje, 1956; Diggs, 1956; Harris *et al.*, 1956; Walters, 1958; Booker, Scott & Ferguson, 1964).

The first report of involvement of the nervous system in sickle cell disease was made by Sydenstricker, Mulbeim & Houseal (1923) who described a 5-year-old boy with spastic hemiplegia, generalized rigidity, mental dullness and repeated convulsions. Isolated case reports followed (Graham, 1924; Hamilton, 1925; Belle, Kotte & Mitchell, 1927; Cook, 1930; Anderson & Ware, 1932; Kampmeier, 1936). However, the most comprehensive review of the literature on the cerebral manifestations of sickle cell disease was made by Hughes, Diggs & Gillespie (1940) who cited thirty-one patients including six of their own. Other reports in recent years have included Rowland (1952), Hill (1953), Greer & Schotland (1962), Baird *et al.* (1964) and Scott & Ferguson (1966).

The first mention of retinopathy in sickle cell disease was made by Cook (1930) who reported subarachnoid and retinal haemorrhages in a Negro boy of 7 years. Later, Harden (1937) noted dilated and tortuous retinal vessels in two other Negro children, and Edington & Sarkies (1952) described retinal microaneurysms in two young patients in the Gold Coast (Ghana). However, the most exhaustive surveys of sickle cell retinopathy were made by Lieb, Geeraets & Guerry (1959) and by Geeraets & Guerry (1960).

Attention was concentrated only on the gross organic lesions associated with sickle cell disease until 1937 when Bosselman & Kraines reported mental changes in a 13-year-old boy who, after a sickle cell crisis, developed persistent personality changes and restlessness with sudden reversion to infantile mannerisms and tendency to make grandiose statements. Henderson (1950) mentioned two cases of frank hysteria in this disease.

In Nigeria, where sickle cell disease is a major medical problem (Mabayoje, 1956; Edozien, Boyo & Morley, 1960; Hendrickse, 1960, 1965; Brew & Edington, 1965; Cockshott, 1965; Watson-Williams, 1965; Isaacs & Hayhoe, 1967), very little has been written about the neurological lesions associated with it (Mabayoje, 1956). This paper is a survey of the clinical, radiological and pathological aspects of involvement of the nervous system in sickle cell disease as observed in a large medical centre in this country.

MATERIAL

Between 1960 and 1968, 257 Nigerians with homozygous (SS) sickle cell disease were admitted to the University College Hospital, Ibadan. Thirty-three of these patients had neurological disorders, representing an incidence of 12·8%. There were twenty males and thirteen females. The earliest age of onset of neurological disease was 5 months, the latest 30 years, the average age of the thirty-three patients being 6·4 years.

RESULTS

I. *Clinical aspects*

General remarks

Two important observations were made which we found very pertinent to the analysis of the various neurological disorders encountered in sickle cell disease.

In the first place, in this systemic disease, with its marked tendency towards recurrent episodes of crises, the major neurological complications tended to be repetitive and multiple, so that one patient may suffer repeated attacks of the same syndrome, or more than one neurological lesion may coexist in a sickler at a particular time, or at different periods. Hence the recorded neurological complications numerically transcended the population of the affected patients (Table 1).

In the second place, while sickle cell disease was responsible primarily for some major neurological syndrome, the finding of the sickling phenomenon and a neurological disease

TABLE 1. Relative frequency of neurological disorders in sickle cell disease (thirty-three patients)

Group	Disease		No.
A. Principal neurological complications	Bacterial meningitis		20
	Cerebrovascular accidents		10
	Occlusive	7	
	Haemorrhagic	3	
	Cranial nerve lesions (optic atrophy, oculomotor palsy, abducens palsy)		3
	Mental changes		2
	Paraparesis		1
B. Secondary neurological complications	Post-meningitic syndromes		9
	Hydrocephalus	3	
	Subdural effusion	3	
	Deafness	2	
	Blindness	1	
	Meningism		3
	Tonsillitis	2	
	Pneumonia	1	
C. Other neurological disorders	Retinal changes		4
	Proptosis		3
	Wilson's disease		1
	Congenital hydrocephalus		1
	Poliomyelitis		1

may be coincidental and not aetiologically related. Thus, in this study, three types of neurological syndromes were encountered: *principal* neurological complications; *secondary* or late results of the principal complications, and *coincidental* neurological disease presumably of independent aetiology. These neurological disorders were as summarized in Table 1.

Presentation of the principal neurological complications

Intelligence was found to be normal in general in these patients who were assessed only by their verbal skill, and in the case of students also by their school grade placement. There were records of class positions in three students—two girls each 15 years old, placed second in a class of forty and fifth in another of thirty-nine respectively; and a boy of 13

who was placed twenty-second in a class of fifty-one. This boy with the relatively poor school record suffered frequent absenteeism as a result of repeated sickle cell crises, much to the detriment of his schooling.

Mental changes. There were two instances of mental disturbance. One was *behavioural disorder* in a boy of 8 years who after recovering from a sickle cell crisis, became uncontrollably aggressive. He fought at school, behaved disgustingly at home and was very destructive. He was placed on amphetamine with benefit. The other example was *hysterical manifestation* in an 11-year-old girl who complained of paralysis of her arms and legs every time she had a pain in a crisis. She was treated successfully with chlordiazepoxide (Librium) and prochlorperazine (Stemetil).

TABLE 2. Prognostic importance of disturbance of consciousness in sickle cell disease

Level of consciousness	Clinical findings	CSF findings	Outcome
Stupor	Known sickler, meningitis	Turbid pneumococcus	Died
Stupor	Known sickler, meningitis	Turbid tubercle bacillus	Died
Coma	Right hemiplegia	Normal	Survived
Stupor	Left hemiplegia	Normal	Survived
Coma	Subarachnoid haemorrhage	Uniformly blood-stained	Died
Coma	Subdural haematoma	No record	Died

Paraparesis. The solitary instance of paraparesis was a known male sickler whose only complaint was of bilateral weakness of the legs, and on examination was found to have spastic paraparesis with posterior column sensory loss. He made spontaneous but slow recovery over a period of 6 months.

The most important major neurological complications noted were *cerebrovascular accidents* and *bacterial meningitis* (Table 1). Two important presenting signs which were recorded in patients with these complications were *disturbance of consciousness* and *convulsive seizures.*

Six patients (18%) in the series were admitted with altered consciousness, three each in stupor and coma. Four of them died in hospital (Table 2), and the two who survived had normal CSF. It would appear that severe alteration in level of consciousness carries a bad prognosis, which is worsened by the presence of serious associated disease and an abnormal CSF.

Convulsions were encountered in sixteen patients, comprising ten males and six females, whose ages ranged from 8½ months to 10 years. Four of these patients had cerebral vascular complications which presented as hemiplegia in three cases and as subdural haematoma in the fourth patient. All of these four had normal CSF. The remaining twelve had abnormal

CSF due to meningitis. There were three deaths in this group of sixteen patients, one from massive subdural haematoma, and two from overwhelming meningitic infections.

Cerebral vascular lesions. The distribution of the ten lesions in this category is shown in Table 3. Sixty per cent of them presented with hemiplegia or hemiparesis resulting from

TABLE 3. Cerebral vascular lesions in sickle cell disease

Lesion	No. of patients	No. of deaths
Cerebral infarction	6	1
Subarachnoid haemorrhage	2	2
Subdural haematoma	1	1
Dural sinus occlusion	1	1
Total	10	5

TABLE 4. Manifestations of cerebral infarction in sickle cell disease

Case No.	Age and sex	Presenting features	CNS findings	CSF picture	Outcome
1	10, F	Afebrile; right-sided Jacksonian fits; fully conscious	Right hemiplegia	Normal	Survived; discharged 13 days after admission
2	14, M	Suddenly dropped down while watching football match; afebrile; generalized epileptiform fit; comatose	Right hemiparesis	Normal	Survived; discharged 6 days after admission
3	7, F	Woke up one morning with left-sided weakness; afebrile; no convulsion; fully conscious	Left hemiplegia	Normal	Survived; slow return of power in left limbs
4	6, F	Afebrile; no convulsion; fully conscious	Right hemiplegia	Normal	Survived
5	2, M	Febrile; right-sided Jacksonian fits; fully conscious	Right hemiplegia Aphasia	Normal	Survived
6	8, M	Febrile; generalized fits; stuporose	Left hemiplegia	Normal	Survived

cerebral infarction. There was equal sex distribution, and the ages of the six patients ranged from 2 to 14 years, with an average of 7·6 years.

Table 4 shows the mode of presentation of cerebrovascular accident (CVA) in the six patients with hemiplegia or hemiparesis. In all of them, the manifestation of the neurological lesion was the initial complaint that brought them to hospital, and the haemoglobinopathy was only discovered during the course of investigation. Where the history

was more informative as in *Cases 2* and *3*, the onset of hemiplegia was sudden. All had normal CSF findings and survived their initial attacks.

In three cases, however, the repetitive or recurring nature of CVA in sickle cell disease and the poor prognostic implication of such an occurrence, were exemplified. *Case 1* recovered fully from her hemiplegia; 6 years later, she came to hospital in deep coma in a crisis, and died 5 days after admission. Post mortem examination showed recent subarachnoid haemorrhage over the right frontal and parietal cerebral lobes.

At the age of 3, *Case 4* had suffered a left hemiparesis at home from which she recovered completely after 4 weeks. One year later, she had right hemiplegia which brought her to hospital. She made only a partial recovery; 2 years later she had yet another CVA which left her with severe right hemiplegia. For the first time she suffered right-sided convulsive seizures and acute pain in the weak limbs.

Case 5 was left with a residual limp after his right hemiplegia. Two years later, he came in in a crisis, comatose and twitching on the right side. He had a dense right hemiplegia and a haemoglobin level of 10%. He received whole blood transfusion, during the course of which he suddenly collapsed and died.

The remaining instances of CVA included a second patient with subarachnoid haemorrhage with heavily and uniformly blood stained CSF who died in hospital; a boy of 15 years with extensive and acute intracranial subdural haematoma who died on the day he was admitted, and another fatal case who at autopsy had thrombosis of the left lateral sinus (Table 3). All came to hospital comatose.

Bacterial meningitis. Nineteen patients (ten males, nine females) had bacterial meningitis. Their ages at the time of presentation varied from 5 months to 15 years, but most of them (63%) were under the age of 2 years (Fig. 1).

Meningitis was the presenting disease in twelve of these nineteen patients. All of the nineteen patients were fully conscious on admission, except two who were comatose. Both died in hospital. Convulsions were observed in twelve patients. All except one had abnormal CSF, and the bacteriology of the meningitic infection was as shown in Table 5. The commonest organisms were the pneumococcus, and *Haemophilus influenzae*. One patient had two attacks of pneumococcal meningitis, the second 4 months after the first attack.

The only two fatalities were the two patients who came into hospital semi-comatose, one with pneumococcal, and the other with tuberculous meningitis. Both were known sicklers. The average duration of hospital stay of the seventeen survivors was 14·3 days. The post meningitic sequelae recorded were subdural effusion (three), internal hydrocephalus (three), deafness (two), and blindness (Table 1).

Other important neurological complications and disorders

Hydrocephalus. Three of the four cases with internal hydrocephalus were post meningitic (*H. influenzae*, two; pneumococcus, one), and the fourth was of the congenital type.

Meningism was found in three patients, all males, aged 1 year, 8 and 12 years. Two had tonsillitis, and the third, pneumonia. They all presented with fever, generalized body and nuchal pains. In one, Kernig's sign was negative and Brudzinski's positive; and vice-versa in the other two. In all of them, the CSF was clear, acellular and under increased pressure with protein content of less than 10 mg % in two patients and no record in the third. They responded quickly and satisfactorily to appropriate chemotherapy.

Cranial nerve lesions. There were five instances of cranial nerve dysfunction, three of which were considered to be primarily due to sickle cell disease on the basis of ischaemia resulting from vascular occlusion. One boy was aged 3 when his haemoglobinopathy was diagnosed. At the age of 5 years, he became blind and was later found to have optic atrophy. A girl of 11 years, a known sickler, presented with an isolated right oculomotor palsy which gradually resolved over a period of 5 weeks. Another girl of 8 years, with histologically

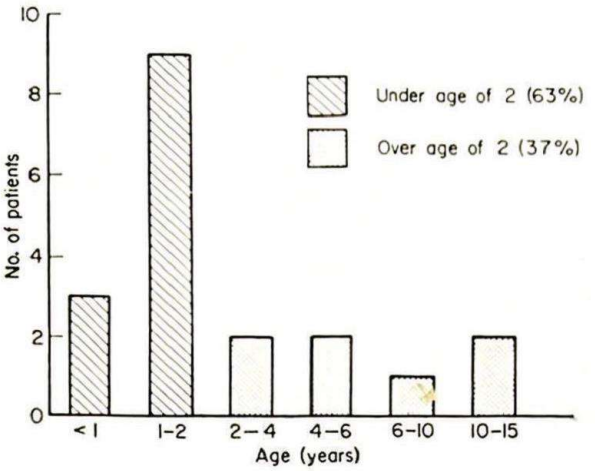

FIG. 1. Age distribution of patients with meningitis.

TABLE 5. Aetiological types of meningitis in sickle cell disease

Types	No. of cases
Pneumococcal	7
Haemophilus influenzae	5
Pyogenic (no organisms)	3
Lymphocytic	1
Tuberculous	1
Meningococcal	1
No organism	1

proven juvenile cirrhosis with intrahepatic cholestasis, developed a sixth nerve palsy which also spontaneously corrected itself after 8 weeks. The remaining two patients—a boy of 4 years and a girl of 7 years, who presented with bilateral nerve deafness both had antecedent bacterial meningeal infections.

Ocular changes. Three patients, all males, aged 5, 16 and 29 years, presented with bilateral *proptosis.* One important observation made in one 8-year-old female was the presence in the cornea of Kayser–Fleischner ring. In this patient, who probably had *Wilson's disease,* liver biopsy confirmed juvenile cirrhosis with intrahepatic cholestasis.

Other coincidental neurological lesions noted included one instance of *poliomyelitis*

which presented with foot drop, and four cases of *retinal* vascular congestion and tortuosity.

II. *Radiological aspects*

Carotid angiography was performed on five patients in the series, two of whom also had cisternal pneumoencephalography. The indications for angiography were hemiplegia and

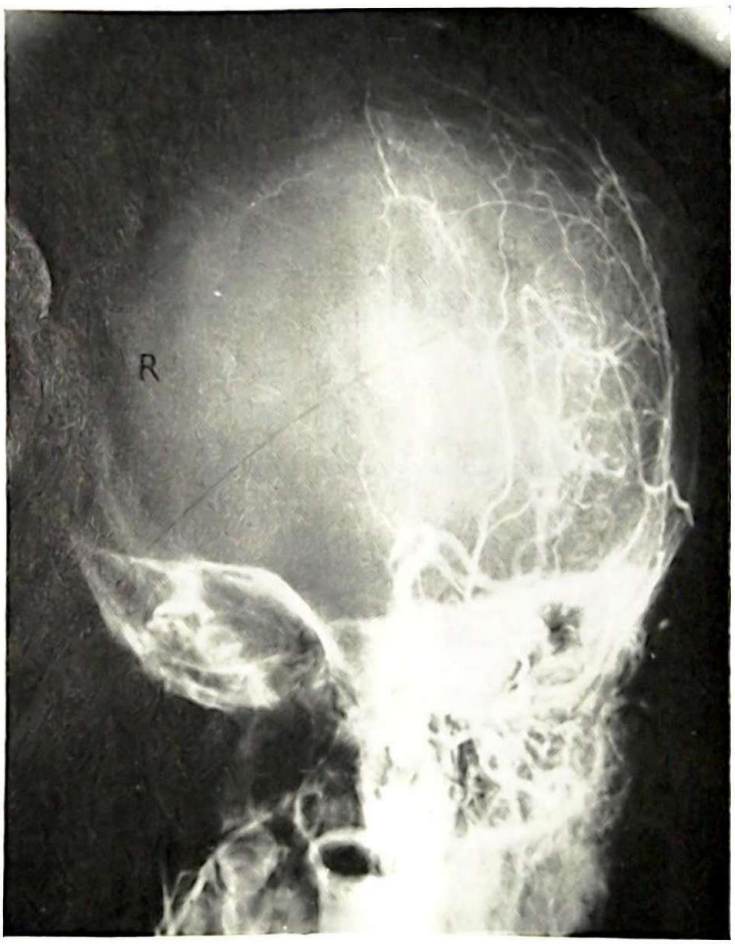

FIG. 2. Antero-posterior view of left internal carotid angiography (Case 7), showing occlusion of the left anterior cerebral artery.

hemiparesis (three), disturbed consciousness and decerebrate rigidity following *H. influenzae* meningitis (one) and decerebrate rigidity only (one). Two of these patients had negative angiographic findings, and the others had positive findings. One of the three patients with hemiparesis showed non-filling of the anterior cerebral artery, the patient with post meningitic drowsiness had internal hydrocephalus and there was intense vascular spasm of the extracranial circulation and non-filling of the anterior and middle cerebral vessels in the

1-year-old boy with decerebrate rigidity. Two illustrative case reports of patients with positive findings are given immediately below.

Case 7. Girl aged 2 years presented with fever and sudden weakness of right arm and leg. On examination, she was fully conscious. Had right spastic hemiparesis, worse in the leg than the arm. Genotype was SS.

Left carotid angiography showed non-filling of the left anterior cerebral artery (Fig. 2).

The angiographic finding was of interest as it explained the pattern of weakness observed clinically. At subsequent follow-up clinics, this girl has shown gradual recovery of her limb weakness.

Case 8. Eleven-year-old girl admitted with *H. influenzae* meningitis. Responded to appropriate antibiotics. Genotype SS. Four weeks after admission, developed akinetic mutism and decerebrate rigidity. Intracranial abscess suspected.

TABLE 6. Analysis of fatal cases

Pathological lesion	Total patients	No. of deaths	Percentage mortality
Subarachnoid haemorrhage	2	2	100
Subdural haematoma	1	1	100
Lateral sinus thrombosis	1	1	100
Cerebral thrombosis	6	1	16·6
Bacterial meningitis (TB, pneumococcus)	19	2	10·5

A left carotid angiography showed non-filling of the left anterior cerebral artery. A right internal carotid angiography performed a week later showed that both anterior cerebral arteries filled from this side and they were bowed and stretched in a wide sweep in conformity with internal hydrocephalus (Fig. 3). Later cisternal air encephalography showed dilatation of the lateral ventricles, the right more so than the left (Fig. 4a, b). A marked internal hydrocephalus was found in the boy with decerebrate rigidity when he had cisternal pneumoencephalography.

III. *Pathological aspects*

Analysis of fatal cases. These are summarized in Table 6. There were seven deaths, representing a mortality of 21·2%, with approximately equal sex distribution. Each of subarachnoid haemorrhage, subdural haematoma and dural sinus thrombosis in our series carried 100% mortality, cerebral infarction 16·6% and meningitis 10·5%.

Three of these seven patients were comatose on admission. In only two patients were there records of autopsy. One had recent subarachnoid haemorrhage over the right frontal and parietal cerebral hemisphere, with antemortem thrombi in a few of the cortical vessels close to the arachnoid granulations; the other had antemortem clot in the left lateral sinus with complete occlusion of the affected vessel.

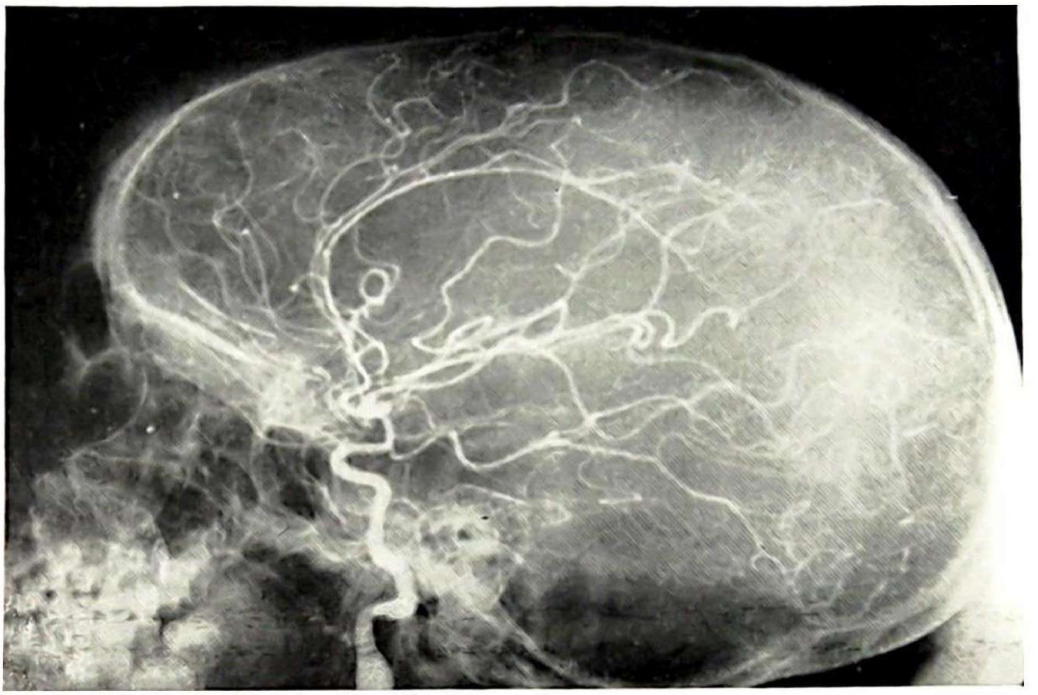

FIG. 3. Lateral view of right internal carotid angiography (Case 8). Note the bowing and stretching of the anterior cerebral vessels due to internal hydrocephalus.

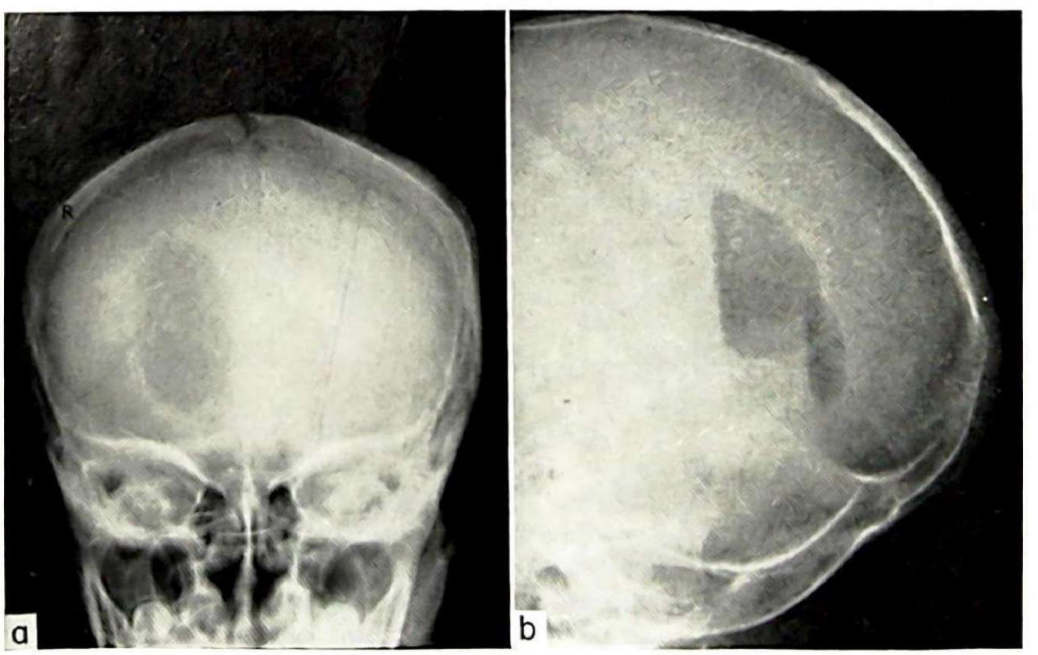

FIG. 4. Cisternal air encephalography in Case 8, showing dilatation of lateral ventricles, the right more than the left. (a) Antero-posterior view; (b) lateral view in brow-down position.

DISCUSSION

It is generally accepted that the nervous system can be involved during the course of sickle cell disease (Hughes *et al.*, 1940; Ballard & Bondar, 1957; Scott & Ferguson, 1966), but the recorded incidence of these neurological manifestations has been very variable. Thus, Patterson, Wilson & Diggs (1950) in 142 patients found fifty-seven (40%) with signs and symptoms referable to the nervous system, Rowland (1952) twenty-seven in ninety-two patients (29%) and Greer & Schotland (1962) seventy-two out of 400 patients (18%).

Of all the haemoglobinopathies it is in the homozygous SS disease that the nervous system seems most vulnerable. In the series of 400 patients with abnormal haemoglobins analysed by Greer & Schotland (1962) eighty-six had homozygous SS disease; yet thirty of the seventy-two patients with neurological disorders were SS. Lieb *et al.* (1959) in sixty-five patients with haemoglobinopathies found three with neurological involvement, all of whom were homozygous SS. Seven of the eight patients with sickle cell disease with neurological manifestations reviewed by Baird *et al.* (1964) had homozygous SS disease. In our series which consists only of SS disease, the incidence of neurological involvement was 12·8%.

Males and females were equally susceptible; and the age of the patients at onset of neurological disease varied widely; from 6 months to 47 years in the series of Greer & Schotland (1962) and from 5 months to 30 years in ours.

Mental changes, though rare, have been documented in sickle cell disease (Bosselman & Kraines, 1937; Henderson, 1950) and were manifested by two of our patients. Intellectual impairment as a rule does not occur in this disease so that patients should enjoy the privileges of a normal person. Mabayoje (1956) described as 'brilliant at school' Case 46 of his series; Baird *et al.* (1964) got poor results on intelligence testing in three of their eight patients, which they attributed to recurrent absenteeism and not mental retardation. Indeed, a year before, Chodorkoff & Whitten (1963) resolved any doubts in a detailed study of the intellectual status of nineteen children with sickle cell anaemia, and came to the conclusion that the disease does not in itself alter the intellectual make-up of a patient.

It is recognized that ocular complications are common in sickle cell disease. Lieb *et al* (1959) found retinal lesions in 90% of their fifty-one patients with homozygous SS disease. The various lesions described included tortuosity and dilatation of retinal vessels, microaneurysms (Harden, 1937; Edington & Sarkies, 1952), stasis and thrombosis of retinal venules; retinal oedema and sausage-like dilatation of fine vessels (Goodman, Von Sallmann & Holland, 1957), retinal and periretinal, and vitreous haemorrhages (Verhoeff, 1947; Greer & Schotland, 1962), papilloedema (Lieb *et al.*, 1959) and angioid streaks in the retina (Geeraets & Guerry, 1960). These various retinal changes usually began at the periphery so that permanent visual impairment is usually late. However, in sickle cell trait, central retinal artery occlusion has been described (Conrad & Penner, 1967) and monocular blindness was reported from Ghana (Konotey-Ahulu, 1968b). Leib *et al.* (1959), in their very detailed study of the ocular lesions in sickle cell disease, classified the observed fundal pathology into four categories according to their severity.

Huck (1923) was the first to recognize the unusual susceptibility of these patients to infections, particularly tonsillitis and pneumonia which were associated with meningism in three of our patients. Our incidence of meningism of 9% is low in comparison with the 33% recorded in homozygous sickle cell disease by Greer & Schotland (1962). A rare cause of this phenomenon is fat embolism. Wade & Stevenson (1941), in reporting such a case,

reiterated the contention of Graham (1924) that the marrow of a necrotic bone in sickle cell disease may well be the source of the emboli. Furthermore, fat embolization in this disease may cause multiple neurological signs depending on the cerebral localization of the emboli (Skoog, 1940), and occasionally it may be fatal (Vance & Fisher, 1941).

Porter & Thurman (1963) mentioned that infections were the major presenting problem in sickle cell disease during the first year of life. Whereas the association of this disease and systemic salmonella infections, especially osteomyelitis, is well known (Hook *et al.*, 1957), its association with pneumococcal meningitis was first suggested by Robinson & Watson (1966), although it was recognized in a Nigerian woman in 1965 (Anon., 1965). The incidence of meningitis in sickle cell disease is variable. Greer & Schotland (1962) mentioned five cases in 400 haemoglobinopathies (1·25%), Robinson & Watson (1966) sixteen out of 252 patients (6·3%) and in the present series, nineteen out of 257 (7·2%). In all these reports, the pneumococcus predominated, accounting for 87% of bacterial meningitis in sickle cell anaemia in the series of Robinson & Watson in comparison with the 26% it caused in the general paediatric population. It has been shown that *Haemophilus influenzae* Type B is the commonest cause of bacterial meningitis under the age of 2 years, and the pneumococcus the most frequent etiological agent after the age of 5 (Robinson & Watson, 1966). Hence it is remarkable that 63% of our meningitic patients and 61% of those of Robinson & Watson (1966) were under the age of 2. These latter authors, impressed by the striking coincidence of pneumococcal meningitis and sickle cell disease, suggested that there may be an interference with pneumococcal antibody production in sickle cell disease.

It is, however, as a veritable cause of cerebrovascular accident in children that sickle cell disease is pre-eminent. Indeed, clinical features indicative of CVA may be the inaugural manifestation of sickle cell disease, an observation first made by Bridgers (1939) and confirmed by others (Mabayoje, 1956; Greer & Schotland, 1962). In all our six patients with hemiplegia this cerebrovascular disorder was the harbinger of their haemoglobinopathy. The pattern and outcome of the CVA is variable, ranging from single episodes with complete recovery to repeated attacks with severe neurological sequelae. Attacks may be transient and reversible, or irreversible; and the clinical effects produced depend on the size of involved vessel and the absence or presence of collateral circulation (Scott & Ferguson, 1966). Kampmeier (1936) first described a boy with repeated symptoms referable to the central nervous system which caused residual limb weakness. When such repetitive attacks supervene, later ones tend to be more severe (Hughes *et al.*, 1940; Case 5 in our series) and their anatomical location may even vary causing different syndromes in consecutive attacks (Bloch, Waldron & Cogan, 1951).

Intracranial haemorrhage and involvement of the dural sinus appear to carry a poor prognosis in most series. The first report of subarachnoid haemorrhage in association with sickle cell anaemia was by Cook (1930) who described a Negro boy who died following sudden loss of consciousness in whom autopsy showed subarachnoid haemorrhage with cerebral softening. Seven years later, Yater & Hansmann (1937) described a negress who at autopsy showed evidence of recent diapedes of red blood cells into the meninges over her right cerebral hemisphere. Since these pioneer works, subarachnoid haemorrhage has maintained a generally poor prognosis as shown by its recorded high mortality of 75% in the four patients of Greer & Schotland (1962) and 100% in our two patients.

A rare lesion but of grave import is dural sinus thrombosis. Ford (1937) mentioned its occurrence in many negro children with sickle cell anaemia, and Schenk (1964) described a

patient who developed frontal headache following tonsillectomy and later had grand mal epilepsy, sixth and seventh cranial nerve palsies, hemiparesis and persistently raised intracranial pressure. At autopsy there was thrombosis of the superior sagittal sinus. Schenk was puzzled about the isolated involvement of this sinus. The solitary example of dural sinus occlusion in our series, like that of Schenk (1964), had a fatal outcome, and autopsy showed that only the left lateral sinus was involved. If we marvel less than Schenk about the anatomical distribution of dural sinus thrombosis, it is because the collation of our experiences leads us to infer that any of the dural sinuses can undergo thrombotic occlusion. Also, it is probable that thrombosis of any of the major sinuses, which suddenly interferes enough with CSF dynamics, can lead to grave neurological disturbance and a fatal termination in sickle cell disease.

There have been reports of electroencephalographic (EEG) studies in sickle cell disease (Hill, Hughes & Davies, 1950; Hill, 1953). Hill *et al.* (1950) reported EEG findings in thirty-eight patients, twenty-six of whom had abnormal records. Abnormal EEG changes were found in all patients in crisis, in all children under the age of 6 years and in some patients with no demonstrable cerebral manifestations. This high yield of positive findings may not be all that significant as there is no evidence that the recorded EEG changes are specific to sickle cell disease; besides, since most of the patients investigated were children, it is possible that some of the anomalies recorded were 'maturational' defects.

Carotid angiography has also been employed in investigating some of these patients, but with less dramatic positive results. Ende, Pizzolato & Ziskind (1955) used it in one of their four patients and found what was suspected as a mid-temporal parietal space occupying lesion, a previous ventriculographic study having shown moderately big lateral and third ventricles. Ballard & Bondar (1957) got negative results in investigating a spontaneous subarachnoid haemorrhage in a sickler. Although a sickling phenomenon was the probable cause in this case, it is worth remembering that a berry aneurysm may coexist with sickle cell disease (Wertham, Mitchell & Angrist, 1942; Cheatham & Brackett, 1965) requiring angiographic studies for its identification. Unfortunately, *in vitro* studies have shown that significant sickling does occur when sickle cell blood (SS haemoglobin) is mixed with hypertonic solution such as the contrast materials used in angiography (Cheatham & Brackett, 1965; Konotey-Ahulu, 1966; Roberts & Smith, 1966), even at the oxygen tension of room air, and at normal body temperature and pH (Perillie & Epstein, 1963).

The cerebrovascular accident in sickle cell disease is commonly precipitated by a crisis, and less often it may follow surgery under general anaesthesia, transfusion of blood, and it may supervene in the post-partum period. That these cerebrovascular lesions could be casually related to sickle cell disease was not mentioned until 1935 when Arena invoked the phenomenon of vascular occlusion—a common tendency in sickle cell disease—to explain the right-sided hemiplegia in a 6-year-old negro boy. 'If such a tendency were present, might it not follow that occasionally the cerebral vessels are involved?' Indeed, Bridgers (1939) confirmed Arena's suspicion when he found the lumina of the middle and anterior cerebral vessels occluded in a young patient who died from sickle cell disease and Bauer (1940) and Bauer & Fisher (1943) suggested that vascular occlusion could occur independently of anaemia as a result of sickling tendency alone. Yet it was only in recent years that this phenomenon came to be recognized as the main factor in the pathogenesis of sickle cell disease (Margolis, 1951; Diggs & Vorder Bruegge, 1954; Diggs, 1956). Diggs (1956) of Memphis, Tennessee, became amply convinced of this fact after observing 747 sickle cell

crises in 166 patients without evidence of increased haemolysis in any one. Furthermore, Walters (1958) found that haemolytic crises are rare in the course of sickle cell disease among Nigerians, while infarction is dominant, following vascular blockage by plugs of sickle cells on which a thrombus forms (Harris *et al.*, 1956). That this vascular occlusion may involve a major cerebral artery has been angiographically demonstrated in our current series.

Certainly, we have gone a long way in our understanding of sickle cell disease since the pioneer days of Herrick in 1910. Anaemia, a common finding in sickle cell disease 'is not the essential and not the most dangerous sign of this disease' (Bauer, 1940; Thompson, Wagner & McLeod, 1948). On the other hand, the marked tendency to spontaneous vascular occlusion encountered makes any system of the body vulnerable, especially the nervous system with its acute sensitivity to hypoxia. It is this potential for presenting in a variety of ways, and in so doing masquerading as other clinical syndromes that stamps sickle cell disease a truly great imitator.

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