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M. I. LEVENE

Department of Paediatrics, Charing Cross Hospital, Fulham Palace Road, London W6.

Neurological complications of β -thalassaemia major

A variety of neurological complications following vascular thrombotic crises have been documented in patients with sickle cell anaemia (Weatherall and Clegg, 1971), but β -thalassaemia major neurological manifestations are uncommon. We report 2 cases of β -thalassaemia major with transient major motor seizures; in one there was in addition transient hemiparesis. The probable pathogenesis of these neurological episodes is considered and the literature on the matter briefly reviewed.

Case reports

Case 1. An 8-year-old Indian boy with homozygous β -thalassaemia major on regular blood transfusions every 6 weeks, was seen on 10 January 1975 with Hb 2.2 g/dl. He was given 70 ml packed cells and Hb rose to 13.9 g/dl.

After the transfusion he developed fever and cough; 5 days later he complained of headache and vomiting. On 18 January he had twitching of his right hand followed by a generalized major fit. He had further fits at 10-minute intervals; they were controlled with intravenous diazepam. On examination he was unresponsive; there was no meningism, localizing neurological signs, or other abnormalities apart from an enlarged liver and spleen. Blood pressure was 120/80 mmHg, temperature 37.2°C, and heart rate 140. Hb was 12.2 g/dl, total white cell count 7100/mm³ (7.1×10^9 /l) with polymorphonuclear leucocytes 80%; platelets were adequate, and a blood film for malarial parasite was negative. Cerebrospinal fluid (CSF) contained red blood cells 1160/mm³, WBC 4/mm³ (lymphocytes), sugar 96 mg/

100 ml (5.33 mmol/l), and protein 0.45 g/l. Serum iron was 268 μ g/100 ml (48 μ mol/l), transferrin saturation 87.5%, and TIBC 306 μ g/100 ml (54.8 μ mol/l).

An electroencephalogram (EEG) on 4 February showed medium-voltage 6-8 cps waves over the right posterior head region: intermittently a 6 cps rhythm was observed over the corresponding area of the left side. Bursts of high-voltage rhythmic 3-4 cps waves intermixed with arrhythmic 2-3 cps delta-waves were seen over the left hemisphere maximally over the posterior quadrant. High-voltage single sharp waves occurred over the left posterior and middle temporal regions.

No further fits were noted after admission. The patient recovered later the same evening and was discharged home after a few days.

Case 2. A 6-year-old Malay girl with homozygous β -thalassaemia major and on regular blood transfusion every 6 weeks, was seen on 23 July 1975 with Hb 3.1 g/dl. She was given 450 ml packed cells after which Hb rose to 11.3 g/dl. On 27 July she had vomiting and diarrhoea; she went to bed and was later unable to walk. On examination there was nystagmus to the right, and left hemiparesis with twitching of the left hand and foot. Temperature was 37.2°C, heart rate 180, BP 110/90 mmHg. Liver was 4 cm, spleen 3 cm; both plantar responses were extensor. Hb was 9.9 g/dl, total white cell count 12 600/mm³ (12.6×10^9 /l), polymorphonuclear leucocytes 72%, lymphocytes 21%; platelets 83×10^9 /l. CSF was normal. She recovered later the same day and received a further blood transfusion which raised Hb to 15.3 g/dl.

On 3 August 1975 she developed fever, twitching of the right hand followed by a generalized major fit. She was found unresponsive with BP 115/65, and no abnormal findings apart from hepatosplenomegaly. Hb was 12.9 g/dl, total WBC 8700/mm³ (8.7×10^9 /l), and platelets adequate. CSF was normal. Serum iron was 200 μ g/100 ml (35.8 μ mol/l), transferrin saturation 84%, and TIBC 238 μ g/100 ml (42.6 μ mol/l). Serum antibody to Arbor virus groups A and B and Japanese B were negative. Serum antibody titre to *Herpes simplex* was <1/8. She was treated with dexamethasone and diazepam for 48 hours and had no further fits.

The first EEG on 30 July showed low- to medium-voltage rhythmic 4-6 cps rhythms over the posterior head regions, more persistently over the left side. β -rhythms were more prominent over the left hemisphere. High-voltage arrhythmic 0.75-3 cps delta-waves were seen intermittently over the right posterior temporal, mid-temporal, and parietal regions. During sleep high-voltage single sharp waves oc-

Table Reported cases of neurological complications in homozygous β -thalassaemia

Authors	No. of cases	Presentation					
		Convulsive seizures	Cerebral manifestations	Cerebellar features	Ataxia	Ischaemic manifestations	Miscellaneous
Davison & Wechsler (1939)	1	—	—	—	—	—	Features akin to Wilson's disease
Portier <i>et al.</i> (1952)*	1	1	—	—	—	—	—
Cruz Valasco (1961)*	1	1	—	—	—	—	—
Gatto (1967)†	1	—	Hemiplegic with systemic bleeding manifestations	—	—	—	—
Orsini <i>et al.</i> (1967)	4	3	—	—	1 (arm)	—	—
Behrakis <i>et al.</i> (1968)*	11	(—)	(—)	6	(—)	(—)	(—)
Logothetis <i>et al.</i> (1972)	38	11	2 vascular strokes with hemiparesis	1 hemiparesis	—	26	—
Present series	2	2	—	—	—	—	—

* Cited by Logothetis *et al.* (1972).† Cited by Orsini *et al.* (1967).

(—) = details unavailable.

curred over the right temporal areas, and frequent sharp-and-wave or spike-and-wave epileptic discharges over the right occipital region. A repeat EEG on 6 January 1977 showed considerable improvement.

Discussion

The Table summarizes reported cases of homozygous β -thalassaemia with neurological disorders. Including our Case 2, a total of 4 cases of hemiparesis has been reported. Of the 2 cases reported by Logothetis *et al.* (1972), one was a 5 year old who developed transient postictal hemiparesis after splenectomy; the second was a 16-year-old girl with Hb 5.7 g/dl who after receiving two transfusions of packed cells developed right hemiparesis and a profound personality change a week later.

Convulsions were noted in 8% of cases studied by Logothetis *et al.* (1972), and in 2 of 24 cases studied by us over a 4-year period. Most of the episodes were isolated or rare and did not require continued anti-convulsant therapy.

Neuropathological studies in β -thalassaemia major by Witzleben and Wyatt (1961) disclosed no changes except for hemosiderin deposits in the choroid plexus; Davison and Wechsler (1939) reported degeneration in the pallidum and striatum. Pneumoencephalographic abnormalities have been interpreted as indicative of cerebral atrophy (Behrakis *et al.*, cited by Logothetis *et al.*, 1972).

The acute onset of the ictus, its rapid resolution to normal, and the lack of meningeal involvement in both our cases suggest an acute vascular episode.

The transient nature of the hemiparesis and coma makes cerebral haemorrhage or arterial occlusive cerebral infarction (embolic or thrombotic) less likely. Patients with cerebral haemorrhage are usually ill with more profound neurological deficit. There was no source for cerebral arterial embolism, nor any of the usual clinical accompaniments of arterial thrombotic infarctions in children such as tonsillar infections, cervical adenitis, neck trauma, and pencil injuries to the throat (Bickerstaff, 1972).

A likely cause for the transient vascular episode in our 2 cases is cortical vein thrombosis. Symptoms of raised intracranial pressure such as severe headache, vomiting, increasing somnolence, convulsions that are focal or generalized, and transient focal neurological signs are common in this form of stroke (Kalbag and Woolf, 1972). The CSF picture can vary from normal to frank subarachnoid haemorrhage. The rapid resolution of the illness is also consistent with this diagnosis. The common predisposing factors for cortical vein thrombosis are paranasal sinus and middle-ear infections, or severe dehydration following gastroenteritis. Case 1 had fever for 5 days and vomiting before the ictus, a situation that could have led to dehydration. Similarly, Case 2 had vomiting and diarrhoea before the ictus. The combination of dehydration and a sudden large rise in haematocrit after blood transfusion may have been sufficient to trigger cortical vein thrombosis in our 2 children whose circulatory systems were probably adapted to a low haematocrit.

Wasi (1977) has stated that thalassaemic patients not infrequently develop hypertension, convulsions, and cerebral haemorrhage after blood transfusion,

but the clinical evolution in our 2 cases does not suggest cerebral haemorrhage. Nevertheless the findings in our 2 patients would reinforce Wasi's recommendations that large and rapid blood transfusion should be avoided in thalassaemic patients who have adapted to life-long chronic anaemia.

Summary

Neurological complications in β -thalassaemia major are uncommon, with cerebral ischaemic episodes related to severe anaemia or convulsions as the most usual manifestations. Two such cases of children of 6 and 8 years are reported. Cerebral venous infarction is advanced as the probable cause of the symptoms. Caution should be exercised in giving rapid, large blood transfusions to thalassaemic patients adapted to long-standing severe anaemia.

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- D. SINNIH, V. VIGNAENDRA, and KAMARUDDIN AHMAD
Departments of Paediatrics and Medicine, University of Malaya.

Correspondence to Dr. D. Sinniah, Department of Paediatrics, University of Malaya, Kuala Lumpur, Malaysia.