THROMBOTIC MICROANGIOPATHY PRESENTING AS A PSYCHIATRIC PROBLEM

BY

K. S. JONES,* M.B., D.P.M.*Senior Registrar in Psychiatry***M. SIM, M.D., D.P.M.***Consultant Psychiatrist*

AND

W. THOMAS SMITH, M.D.*Senior Lecturer in Pathology*

From the Department of Psychological Medicine, United Birmingham Hospitals, and the Department of Pathology, University of Birmingham

The first description of thrombotic microangiopathy (T.M.) is attributed to Moschowitz (1924). The condition was reviewed by Symmers (1952, 1956a), who mentioned that the clinical diagnosis is usually suggested by the following tetrad: fever, haemolytic anaemia, thrombocytopenic purpura, and neurological disturbances which are often of bizarre and fluctuating type. The dominant pathological feature is widespread occlusion of small blood-vessels with eosinophilic thrombi.

References to mental disturbances such as confusion, disorientation, abnormal behaviour, and changes in consciousness have frequently been made—for example, Singer *et al.* (1947), Green and Rosenthal (1949), and Antes (1958). Neuropathy has often dominated the clinical picture, but only occasionally have the initial symptoms suggested a primary psychiatric disorder (Epstein *et al.*, 1948; Goldenberg *et al.*, 1950; Baroness, 1952; Cooper *et al.*, 1952).

We present the following case for three reasons: (1) to draw attention to this misleading and little-known mode of presentation; (2) to show that the abnormal periodic-acid-Schiff (P.A.S.) positive material which Bornstein *et al.* (1960) found around cerebral blood-vessels in T.M. is not present in every case; and (3) to show that cerebral embolism secondary to cardiac vegetations of the Libman-Sacks variety can occur in T.M.

Case Report

A man aged 41 was referred to the psychiatric department of the Midland Nerve Hospital by a neurologist who was unable to find evidence of organic disease. The patient related his symptoms to a car accident 12 months previously in which he sustained mild head injuries; since then he had not worked. Two months after the accident he had been admitted to a local hospital with abdominal pain, jaundice, fever, and anaemia (Hb, 72%; R.B.C. 3,470,000/c.mm.). We found no history of psychopathic heredity or of physical or mental ill-health prior to the accident. There was a depressive element and considerable hysterical overlay, suggesting a compensation neurosis. As an insurance claim was pending he was asked to contact the clinic again when this was settled; he received £3,000, resumed work for two years, and was not seen by us for 31 months, when he returned, complaining of imbalance and depression. He had given up work three months previously. Treatment as an out-patient for four months did not result in improvement; organic disease was suspected, and he was admitted to the Queen Elizabeth Hospital, Birmingham.

Recently there had been several episodes of transient confusion, apathy, general weakness, poor concentration, sudden deterioration of vision in the left eye, and, according to his wife, temporary loss of use of the left leg and right hand, defective memory, headaches, dizziness, anorexia, and a disinterest in his appearance. His depression was worse early in the day.

Examination.—Mentally retarded and passive. Slight jaundice and pallor. Afebrile. Purpura over both shins and right hand. B.P. 170/100; cardiovascular and respiratory systems otherwise normal. Liver palpable 2 in. (5 cm.) below costal margin. Left homonymous hemianopia confirmed by perimetry. Pupils normal. Biceps and supinator jerks brisk, left more than right. Knee-jerks very brisk but equal. Left plantar response equivocal. Babcock sentence: performance poor though some evidence of learning. Kohs blocks: card I, very slow; II and III, good; IV and V failed. Digit span: 5 forwards, 3 in reverse.

Special Investigations.—R.B.C. varied from 2,590,000 to 2,170,000/c.mm. (anisopoikilocytosis and doubtful spherocytosis); Hb from 7.5 to 6.4 g./100 ml., reticulocytes from 4.6 to 9.4%, platelets from 120,000 to 110,000/c.mm., and W.B.C. from 7,700 to 6,500/c.mm.; bleeding-time 5½ mins.; prothrombin 100%; normoblastic corpuscular erythroid hyperplasia with pleomorphism and appreciable numbers of macronormoblasts; E.S.R. 2 mm. in 1 hour (corrected Wintrobe); no L.E. cells; W.R. (blood and C.S.F.) and Kahn test negative; differential sheep-cell-agglutination test and blood culture negative; urine consistently contained 1 g. albumin per litre and occasionally red blood cells, casts, and pus cells; blood urea rose to 138 mg./100 ml. before death; urea concentration did not exceed 1.2% in 89-ml. specimen; serum bilirubin 1.1 mg./100 ml.; serum alkaline phosphatase 23.2 units/100 ml. (Jenner and Kay); van den Bergh indirect positive; chest x-ray examination—inflammatory lesions in right upper and lower zones and left upper zone; sputum, no tubercle bacilli; bronchoscopy showed no evidence of carcinoma; Mantoux positive 1:1,000; C.S.F., no abnormalities; skull x-ray picture normal.

Negative tests included muscle biopsy, stool for occult blood, x-ray examination of long bones and hands, urine for lead and porphyrins, I.V.P.

Course.—The extensive investigations given above indicate the diagnoses considered. The patient was allowed to return home for Christmas, but on Boxing Day he was readmitted as an emergency case. He was pale, jaundiced, and semicomatose. There was purpura over the shins and a left hemiplegia. The temperature rose to 100.2° F. (37.9° C.), and death occurred shortly after admission.

Post-mortem Findings

Purpura and ecchymoses occurred over legs and arms. There was slight jaundice.

Lungs.—Bilateral apical pleural adhesions, fibrocaseous lesions in right upper and lower lobes; fibrous scarring, calcification and caseation of related lymph nodes. No carcinoma.

Heart (480 g.).—Left ventricular hypertrophy and dilatation; crumbly, adherent verrucose vegetations on posterior cusp of mitral valve and tiny firm nodules along lines of closure of both cusps; other valves normal; no mural thrombi.

L. Femur.—Shaft 36.5 cm., upper 15 cm. containing hyperplastic marrow.

No relevant changes were found in the mouth, oesophagus, gastro-intestinal tract, liver, kidneys, spleen, bladder, prostate, testes, adrenals, thyroid, pituitary, cervical and abdominal lymph nodes, peripheral nerves, spinal cord, and limb and trunk muscles. The skull showed no evidence of old fracture.

Brain.—Diffuse atrophy, most marked over frontal lobes. Petechial haemorrhages over cortical surfaces. Cystic softening of right inferior temporal cortex extended backwards

*Now at Morgannwg Hospital, Bridgend, Glamorgan.

FIG. 1.—Myocardium showing intra-arteriolar thrombi and fine intermuscular fibrosis. (Haematoxylin and eosin. $\times 250$.)

FIG. 2.—Posterior cusp of the mitral valve showing fibrosis, the attached hyaline vegetation, and granulation tissue between it and the cusp. (H. and E. $\times 8.5$.)

FIG. 3.—Thrombus in a cortical arteriole: endothelial proliferation and recanalization (H. and E. $\times 450$.)

to involve inferior and medial aspects of right occipital region, including striate area. Occasional small depressed cortical scars involved occipital, parietal, and parasagittal cortices bilaterally. No macroscopical thrombosis of major arteries or venous sinuses. Brain stem and cerebellum normal.

Histology

Microthrombosis affects capillaries, and, to a less extent, arterioles and venules of many organs; thrombi are usually homogeneous and hyaline (occasionally granular), eosinophilic, staining yellow-brown with van Gieson's mixture, pink with the P.A.S. stain, and negatively for fibrin. Many thrombosed vessels show endothelial proliferation, sometimes covering free surfaces of thrombi. Occasional recanalization of thrombi. Outside nervous system, microthrombosis present in kidneys (glomerular afferent arterioles and capillary tufts—associated with endothelial proliferation—and in a few medium-sized renal arteries), adrenals, myocardium (capillary and arteriolar thrombosis—Fig. 1—is associated with focal fibrous scars), spleen (Malpighian and trabecular arterioles), liver (sinusoids), skin (dermis), and small intestines. Thrombi not seen in skeletal muscles, lungs, pulmonary lymph nodes, pancreas, thyroid, testes, prostate, bone-marrow.

Mitral Valve.—Vegetations consist of homogeneous eosinophilic material staining similarly to the microthrombi (Fig. 2). Bacteria not present. Valve cusp fibrosed, showing "fibrinoid" degeneration of collagen, "mucoid oedema," and infiltration with lymphocytes, plasma cells, and occasional polymorphs. Cellular granulation tissue between vegetation and cusp.

Lung.—Inactive fibrocaceous tuberculosis. Acid-alcohol-fast bacilli not found.

Peripheral nerves and spinal cord normal.

Brain.—Widespread occlusion of capillaries, venules, and arterioles of leptomeninges, cerebral cortex, and white matter with microthrombi; occasional recanalization and/or endothelial proliferation (Fig. 3). Areas of early infarction sometimes related to microthrombi. Ischaemic degeneration of neurones, and swelling and loss of myelinated fibres commonly seen around thrombosed vessels, but gliotic micro-infarcts found only in cerebellum. Macroscopical lesions in right occipital and temporal lobes are old cystic cortical infarcts showing dense surrounding gliosis and infiltration with phagocytes containing iron pigment and sudanophil lipid. Insufficient microthrombi seen in relation to these older (macroscopical) lesions to explain their origin. P.A.S. stains show no evidence of diffusion of abnormal material through damaged vessel walls.

Discussion

The histological character of the microthrombi found throughout the body in this case confirms the diagnosis of T.M. as defined and described by the authors previously mentioned. It has often been suggested that the thrombi consist of fused masses of platelets, hence the alternative term "platelet thrombosis syndrome." This question is discussed by Craig and Gitlin (1957), whose work with fluorescent antibodies strongly suggests that the thrombi are in fact composed of a derivative of fibrin or fibrinogen. Diffusion of the abnormal P.A.S.-positive material through the walls of damaged cerebral blood-vessels, described by Bornstein *et al.* (1960), was not present in our case. The frequency with which such diffusion occurs has still to be established.

The jaundice and anaemia found at the time of onset of the disease four years before death must have been an early manifestation of T.M. Although affected patients usually die sooner (Symmers, 1952), longer periods are described, for example eight years by Báez-Villaseñor and Ambrosius (1957). The visual symptoms and signs were difficult to assess clinically,

although homonymous hemianopia due to infarction of the occipital pole has been noted before in T.M. (O'Brien and Sibley, 1958). There seems to be no doubt from the necropsy findings in our case that the sudden deterioration in vision several months before death was due to occipital infarction.

Significant microthrombi were not related to the occipito-temporal infarct, and furthermore would be unlikely to result in confluent neural damage of this degree. Adams *et al.* (1948), in describing the neuropathological changes in T.M., pointed out that neural degeneration secondary to the vascular lesions is usually only slight; definite softening has, however, occasionally been found (Engel *et al.*, 1947; O'Brien and Sibley, 1958). The cerebral infarction in our case can nevertheless be explained. Friable verrucose abacterial vegetations, resembling those of Libman-Sacks endocardopathy, were present on the mitral valve; similar vegetations have occasionally been found previously in T.M. (Engel *et al.*, 1947; Meacham *et al.*, 1951; Barondess, 1952; Vassar and Spain, 1953; Symmers, 1956b); Symmers mentioned that this suggests the possibility of a relation between T.M. and disseminated lupus erythematosus and other "collagen diseases." It is probable, therefore, that the large infarct resulted from embolic occlusion of the right posterior cerebral artery at some point not identified, the source of the embolus being the mitral vegetations. The other smaller, macroscopical scars in the hemispheres, also unrelated to T.M. lesions, were also probably embolic.

The psychiatric picture had two components. The earlier, in 1950, was of a functional nature, while the latter was clearly of organic type, although a functional contribution could still be recognized. It was a non-specific reaction, and without the physical findings the possible nature of its organic origin could not, of course, have been recognized.

In T.M. the fully developed diagnostic tetrad is often found only late in the illness, and if the condition is to be diagnosed early it should be considered when any of the components of the tetrad are found, alone or in combination (Symmers, 1956b). In our patient, fever was noted while he was in hospital four years before his death, but was not found again until just before death. The lowest platelet count was 110,000/c.mm., and did not reach the "critical level" (40,000/c.mm.), although as successive counts may swing between very low and normal figures (Symmers, 1952) we may by chance have missed the lowest value attained.

A positive diagnosis was not made before death; T.M. was nevertheless considered and a muscle biopsy was performed in an unsuccessful attempt to confirm this suggestion. Muscle taken at necropsy also failed to show lesions, indicating that undue significance should not be attached to a negative muscle biopsy in the diagnosis of this disease during life.

In conclusion, we reiterate that this syndrome should be included in the differential diagnosis of obscure encephalopathy with multifarious features; psychiatrists should consider it in conjunction with other unusual vascular diseases which sometimes underlie organic psychosis.

Summary

A fatal case of thrombotic microangiopathy is described which first presented as a psychiatric problem. Typical microthrombotic lesions were found in the brain and other viscera. Verrucose vegetations of the type

seen in Libman-Sacks endocardopathy were present on the mitral valve, and these had resulted in cerebral embolism, with calcarine infarction and homonymous hemianopia. There was no evidence that abnormal P.A.S.-positive material had diffused through damaged cerebral blood-vessels.

We wish to acknowledge the help and advice received from Dr. P. H. Davison, particularly in regard to the clinical investigation of this case.

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HALLUX VALGUS

THE OSTEOTOMY OPERATION*

BY

G. N. GOLDEN, M.D., F.R.C.S.

Surgeon, Orthopaedic and Accident Department,
 Royal Surrey County Hospital, Guildford

It has often been assumed that hallux valgus is caused by wearing too pointed a shoe or one of insufficient length. Whether or not the occurrence of the deformity is thus easily explained is open to question. There can be no doubt, however, that once a valgus angle between the first metatarsal and the great toe has formed, pointed shoes will increase the deformity and make it more painful. The present popular Italian styles in women's shoes must crowd the toes together, and the high heel throws much more than the normal proportion of body weight on the forefoot.

A great increase in the already large numbers of women patients with painful toe deformities, particularly hallux valgus, must therefore be expected. What has surgery to offer for the relief of these conditions? Before considering the operations in common use for the relief of hallux valgus it is advisable to note the characteristic features of this deformity, which are as follows:

The axis of the first metatarsal is not parallel with that of the second and third, and forms with them a varus angle, frequently over 15 degrees, and sometimes 20 degrees or more—metatarsus primus varus. This in itself makes the first metatarsal head prominent (see Fig. 1).

*Read to the Section of Orthopaedic Surgery at the Annual Meeting of the British Medical Association, Torquay, 1960.