Transient Cerebral Ischemic Attacks Associated With Subacute Bacterial Endocarditis

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Abstract:
The case histories are given of 12 patients who had transient cerebral attacks in association with subacute bacterial endocarditis. The attacks are similar to those that accompany atherosclerotic occlusive cerebrovascular disease. All patients had manifestations of general illness, particularly fever, malaise, and elevated sedimentation rate. Subsequently, cerebral infarcts occurred in three patients and cerebral hemorrhages in four patients. A definite relationship between anticoagulant therapy and hemorrhage could not be established.

ADDITIONAL KEY WORDS
anticoagulant therapy

cerebral infarction
cerebral embolism
cerebral hemorrhage

sedimentation rate

Because the occurrence, in patients with subacute bacterial endocarditis, of brief transient episodes of neurological dysfunction that in themselves are similar in all respects to the transient ischemic attacks often associated with atherosclerotic occlusive cerebrovascular disease have attracted little attention, we thought it of interest to record and discuss briefly 12 such cases.

Case Reports

Case 1

This 52-year-old man had aortic stenosis and regurgitation as a result of rheumatic heart disease. On December 8, 1962, his aortic valve was resected and replaced, during temporary extracorporeal circulation, with knitted Bahnson cusps. Penicillin was administered until December 17, 1962. No anticoagulants were used after the operation. Early during the postoperative period, he was extremely ill with pulmonary edema, congestive heart failure, atrial fibrillation, and heart block; later, he improved remarkably. He was afebrile and was to go home on January 2, 1963.

On January 1, 1963, he had an elevation of temperature to 104.5°F. and auscultatory evidence of aortic incompetence. On January 3, *Staphylococcus aureus* was cultured from the blood, and antimicrobial therapy was resumed. On January 4, he had a 15-minute episode of transient numbness and weakness of the left limbs, without involvement of the face. On January 7, a moderate left hemiparesis appeared abruptly; this persisted four or five hours. Despite antimicrobial and cardiac therapy, further valvular incompetence developed, and he died on January 9, from acute ventricular failure and pulmonary edema. Autopsy showed rupture of the aorta at the leaflet, presumably from infection; the brain was normal.

Case 2

A 31-year-old man who had rheumatic fever at 12 years of age was first seen in August 1950. Early that summer, after the removal of several teeth, he suffered recurrent fever, with embolic phenomena to his fingers. Penicillin was administered; however, he had an urticarial reaction, and use of this medication was discontinued before admission.

Examination on admission revealed evidence of aortic insufficiency and of mitral stenosis and insufficiency. Blood cultures revealed *Streptococcus viridans*. The sedimentation rate was 91 mm in one hour (Westergren). Tetracycline and streptomycin were administered. For a week he continued to have occasional embolic phenomena to his fingers and his temperature was intermittently elevated. A week after treatment began, his
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blood culture was sterile; he was asymptomatic and was dismissed.

He was readmitted in November 1950 because of the recurrence of fever, and a few petechiae were noted in his conjunctiva. Blood cultures again grew *Strep. viridans*. Small desensitizing doses of penicillin were administered, along with triplepenamine without untoward effects; later larger doses were used.

On January 25, 1951, he had an episode of severe dizziness, confusion, and difficulty in speaking and in swallowing. He recovered from these symptoms in one hour. On the morning of January 26, he suddenly had a right upper monoplegia, weakness of the right corner of the mouth, and some dysarthria. These neurological abnormalities decreased in severity during the next several hours, although repeated examinations showed minimal weakness of the right side of the mouth to midafternoon, at which time his condition was normal. That evening, he was observed to have a two-hour period of dysphasia. His condition remained normal until January 29, when moderate weakness of the right upper extremity and dysphasia occurred suddenly; these symptoms gradually lessened over the next several weeks, and at the time of his dismissal early in February his condition was nearly normal.

**CASE 3**

A 31-year-old woman was hospitalized on March 26, 1952, with a complaint of malaise and fever. Aside from rheumatic heart disease as a child and hypertension with her three pregnancies, her health had been generally good until December 1951, when, a week after several teeth were extracted, she had fever and dependent edema of the feet. Her physician, who noted a heart murmur and anemia, prescribed penicillin. Her fever subsided temporarily, and when it recurred, oxytetracycline was administered and the fever disappeared again, although only temporarily. For the next several months, she had intermittent fever and was occasionally given antimicrobial therapy.

On admission, examination revealed a chronically ill woman, apical systolic murmur, and regular heart rhythm. Blood pressure was 150/95 mm Hg. Cultures of the blood drawn on the day of admission revealed *Strep. viridans*. Penicillin, dihydrostreptomycin, and whole blood were administered. Anticoagulants were never given.

On April 1 and April 3, she had a one-hour episode of numbness of the right fingers and the right side of the mouth. On April 8, she had a convulsion; afterward, coma, flaccid right hemiplegia, and deviation of her eyes to the left were noted. She died in 12 hours. Autopsy showed hemorrhage in the left frontotemporal region, with rupture into the ventricle. The left carotid and middle cerebral arteries were normal.

**CASE 4**

This 15-year-old boy was seen on October 30, 1956, because of numbness and weakness of the left side of the face. At 11 years of age, he had surgical correction of coarctation of the aorta; when he was studied at that time, mitral insufficiency was also noted.

For several weeks before admission he had cellulitis of the left ankle, fatigue, and low-grade fever. At 9 o'clock on the morning of admission, he experienced quickly a tingling numbness of the left side of the face and, one hour later, numbness of the entire tongue; at 2 o'clock, all symptoms abated. Later that day, weakness of the left side of the face and slurring of speech appeared; these abnormalities were observed on admission and persisted for approximately three hours. Later still in the day, he had a 10-minute episode of numbness of the left thumb and index finger. His temperature was 101°F. Spinal fluid was normal in appearance; it contained 25 mg protein, 12 lymphocytes, three polymorphonuclear cells, and one red cell. Blood cultures grew *Strep. viridans*. Administration of penicillin was started on November 4 and continued for two weeks. At the end of this time, a blood culture was normal. One week after institution of therapy, he had an embolic episode to one finger. He has remained well since except for cardiac symptoms.

**CASE 5**

During the summer of 1953, this 38-year-old man complained of general malaise and two episodes, of three or four minutes each, of faintness; in one episode, he also had had double vision, peri- oral numbness, and numbness of the first, second, and third digits of the left hand. He had had rheumatic fever as a child. When seen in January 1953, he had malaise, fever, and a prominent systolic murmur. Culture of the blood grew *Strep. viridans*. Subacute bacterial endocarditis was diagnosed. Penicillin and streptomycin were administered, and he became afebrile in one week and felt well, and was discharged from the hospital. He died in his home community in July 1954, after an acute illness of 12 hours. A clinical diagnosis of subarachnoid hemorrhage was made on the basis of sudden onset of headache, paresis of the right external rectus muscle, left hemiplegia, stupor, and bloody spinal fluid.

**CASE 6**

A 68-year-old man was seen in June 1956, with a complaint of anorexia, generalized weakness, and episodes of purpura. During the previous fall, he had bronchopneumonia, for which penicillin was administered. In January 1956, cough returned.
and he again took penicillin for one week and felt better. A week after discontinuation of this medication, he had a five-minute episode of difficulty with speech and of clumsiness of his right hand. On February 26, he had a ten-minute episode of awkwardness of his right hand, slurred speech, and poor word choice; two days later, he had another similar episode. At this time, a spinal fluid examination was reported to show many red cells and an elevated pressure. Purpura of his legs was also seen.

On admission, general examination showed a systolic murmur at the apex, heard in the left decubitus position, and a few petechial spots on the lower extremities; results of neurological examination were normal. His temperature was 99.4°F, orally. The hemoglobin value was 8.6 gm/100 ml, erythrocyte count was 3,600,000/cu mm, and erythrocyte sedimentation rate was 99 mm in one hour (Westergren). A blood culture showed *Strept. viridans*. Penicillin was administered. Subsequent blood cultures were negative. Follow-up two years after dismissal revealed that the patient was asymptomatic.

**CASE 7**

This 32-year-old woman was seen in October 1958 because of fever, chills, sweats, and malaise since June 1958. In March 1958, some dental work had been performed. During the summer of 1958, her temperature had increased to 103°F on several occasions and, on three of these, she experienced right visual field scotomata (“faulty” or “blurred”), which lasted about 10 minutes each; the exact time relationships, however, were not recalled. One episode was associated with mild nausea and another with periorbital discomfort; again the sequence of the several phenomena was not recalled. During the fall, she had several (estimated four) episodes of paresthesia and weakness or awkwardness in the left upper limb; each episode appeared abruptly, lasted about 30 minutes, and disappeared in about a minute, and was not associated with headache. She was unaware of any alteration in consciousness with these episodes. Nonetheless, on one other brief separate occasion, she was unable to figure out how to start her car, though other mental functions then were normal.

On admission, the results of her general and neurological examinations were normal apart from a systolic murmur of mitral valve incompetence and a temperature of 99°F. The hemoglobin value was 10.9 gm/100 ml, erythrocyte count was 3,940,000/cu mm, leukocyte count was 7,900/cu mm, and erythrocyte sedimentation rate was 72 mm in one hour (Westergren). A blood smear showed rouleau and toxic polymorphonuclear cells. A blood culture showed *Strept. viridans*.

Treatment with penicillin and streptomycin was instituted on October 24. Subsequent daily blood cultures were negative. On November 2, an embolic phenomenon occurred in the left hallux. On November 3, she took an afternoon nap and on awakening had right hemiplegia, right homonymous hemianopsia, and global aphasia. A clinical diagnosis of cerebral infarct was made. Left stellate ganglion block and intracarotid injection as well as intravenous administration of papaverine were without clear benefit. Administration of penicillin and streptomycin was stopped on November 10. She was afebrile, and blood cultures had remained negative. She was walking with a cane and could say a few words when dismissed from the hospital in March. Examination six years later showed only minimal further improvement.

**CASE 8**

This 15-year-old girl was seen on April 24, 1962, because of fever and a swollen ankle. She had aortic valvular insufficiency as a result of rheumatic fever at five years of age. On admission, laboratory data included hemoglobin value of 9.5 gm/100 ml, leukocyte count of 15,500/cu mm, and sedimentation rate of 88 mm in one hour (Westergren). Her temperature was 102°F. During the first few days, blood cultures grew *Strept. viridans*. She was treated with penicillin and streptomycin. Eight days after the start of this treatment, she had a 30-minute attack of severe vertigo and nausea. Blood cultures at this time were negative. Caloric examination revealed no response on the right side and a reduced response on the left. It was assumed that these were the result of streptomycin, the administration of which was then discontinued.

Although all cultures had been negative since the beginning of treatment, she continued to have periods of fever, and consequently treatment with penicillin had been continued. She was afebrile on May 17 and 18. On the morning of May 19, her temperature was elevated to 101°F. On the evening of May 19, while being examined, she had the abrupt onset of rather severe left parietal head pain, nausea, and vomiting. Within a minute, her speech was slightly slurred and she had poor choice of words. The headache and dysphasia lasted 10 minutes. She was febrile for several days thereafter but then became afebrile. She was dismissed from the hospital several weeks later, feeling well.

**CASE 9**

In the spring of 1963, this 63-year-old man had the “flu” and felt febrile and tired. About this time, he had had some teeth extracted. Because of the persistence of fever, he consulted his physician, a cardiologist, who noted no cardiac
muramur. Blood cultures were negative. The patient was treated with antibiotics. On a follow-up visit one month later, a cardiac murmur was heard for the first time. Blood cultures again were negative. Larger doses of penicillin and streptomycin were administered, and in a few weeks the patient felt well.

He was admitted to our cardiology service in September 1963 in order to assess the advisability of surgical repair of his aortic insufficiency. Examination revealed evidence of severe aortic valvular incompetence. Blood cultures were negative. The hemoglobin value and leucocyte count were normal; erythrocyte sedimentation rate was 37 mm in one hour.

On September 25, 1963, a Starr-Edwards ball-valve prosthesis was placed (temporary extracorporeal circulation). The noncoronary cusp had been destroyed, presumably by the previous endocarditis. From the day of operation until discharge, he received large doses of penicillin. His postoperative course was satisfactory. Anticoagulant therapy (warfarin sodium) was started on the fifth postoperative day (September 30). The dosage was in therapeutic range on October 2. He was dismissed from the hospital on October 8, 1963, and advised to continue therapy with coumarin drugs for several months.

He was readmitted on November 8. His progress had been good until October 23, when malaise and fever appeared. On October 27, his temperature increased to 102°F, and he fainted while walking to the bathroom. He continued to feel feverish and ill. On October 30, he was hospitalized in his home community, where immediate blood cultures grew coagulase-positive Staph. aureus. A few flame-shaped hemorrhages were noted in his conjunctivae. Oxacillin, erythromycin, and chloramphenicol were prescribed. Although he felt that his condition had improved, his temperature remained elevated. Several subsequent blood cultures were also positive. He had continued to receive anticoagulant treatment.

On admission to our service, his temperature was normal. The prothrombin time was in therapeutic range at 41 seconds (normal 17 to 19 seconds). The anticoagulant therapy was permitted to lapse; prothrombin time was 21 seconds on November 13. Methicillin was administered. Blood cultures were negative. He remained afebrile, felt better, and was dismissed on December 4. He was advised to continue the antibiotic program.

On each of the mornings of December 20 and 21, he had an episode of weakness and poor use of the right hand; each was present on awakening and lasted about two hours. He was afebrile. On December 24, he stopped taking the antibiotics because "he ran out of the pills," and on December 29, fever and headache reappeared. He was readmitted to our hospital on December 30, 1963. His temperature was 102°F. On awakening on December 31, he had moderate weakness of the right side of the face and of the right hand; these lasted for several hours and disappeared. An electroencephalogram performed later that day was normal. Blood cultures were again positive, and antibiotic therapy was reinstated. He was transferred to his home on January 27, 1964. He died in the spring of 1964. The report on autopsy indicated no evidence of brain disease, aside from severe atherosclerosis of the major arteries at the base of the brain.

CASE 10

A 34-year-old man was seen on December 21, 1963, because of bloody spinal fluid. He had had elevated blood pressure for at least 12 years. Two weeks before admission, he had a two-hour period of awkwardness of his right upper extremity and inability to write. He believed that his temperature was elevated at that time. He did not consult a physician and took no medicine. One day before admission, he awoke with a fever, headache, weakness of the left limbs, and an unsteady gait, all of which persisted. A lumbar puncture showed bloody fluid. He was given antibiotics because of the elevated temperature. The next day, when admitted to our service, he had a temperature of 102°F, a stiff neck, and moderate left hemiparesis. He collapsed suddenly during the examination, became comatose, and died four hours later. Autopsy showed a massive intracerebral hemorrhage on the right, with rupture into the ventricular system, an enlarged heart, and infection of the mitral valve.

CASE 11

This 69-year-old woman was seen on May 25, 1964. She had a long history of migraine preceded by scintillating scotomata. In 1957, she had a myocardial infarction; anticoagulant therapy was started and was continued for years.

In April 1964, she became fatigued and anorexic, and began to lose weight; she also began to be awakened by a new kind of frontal headache. On May 17, she had an episode, which lasted several hours, of weakness, incoordination, and numbness of the left upper extremity. On admission, it was noted that her memory was poor and she was slightly confused. There was a murmur of mitral insufficiency; she was afebrile. Anticoagulant therapy had been stopped the day after the spell. On admission, her prothrombin time was 22 seconds (normal 17 to 19 seconds). The sedimentation rate was 82 mm in one hour, hemoglobin value was 10.5 gm/100 ml, and temperature was 98.4°F. On May 27, an
Her neck was supple. She became comatose and died. Spinal fluid contained 50 mg protein, one erythrocyte, and 746 erythrocytes, and was slightly yellow. Autopsy was refused.

Comment

The diagnosis of subacute bacterial endocarditis in these cases rests on the presence of cardiac valvular abnormality and septicemia with positive cultures; the latter was noted in all except one patient (case 10) in whom, because of his rapid demise, cultures were not performed and the endocarditis was noted at postmortem. Additionally, all patients were ill with fever and malaise. About half had evidence of other embolic phenomena. Aside from positive blood cultures, laboratory studies showed anemia and elevated leukocyte count in some. An increase in the erythrocyte sedimentation rate was a nearly constant feature, and the rate was often very high.

Rheumatic fever was likely the underlying etiological agent of the valvular abnormality in most of the patients. Atrial fibrillation was seen in only one patient. A possible source of the infection was noted in a few patients.

The incidence of these transient attacks in patients with subacute bacterial endocarditis was low, about 3%, as these 12 patients were drawn from a group of 385 patients with subacute bacterial endocarditis.

The neurological symptoms in these episodes, as well as the episodes themselves, were similar to those noted in patients who have transient cerebral ischemic attacks associated with atherosclerotic cerebrovascular disease. We assume that the transient neurological symptoms are the result of septic emboli arising from endocarditic lesions and going to the brain. We obviously cannot exclude the other causes of transient attacks such as atherosclerosis; one patient (case 9) had severe atherosclerosis at postmortem.

Seven patients (cases 2, 3, 5, 7, 10, 11 and 12), in addition to their transient attacks, had permanent cerebral damage. Three patients (cases 2, 7 and 11) had what appeared to be a nonlethal cerebral infarct. Of these three, only one patient (case 11) had examination of the spinal fluid, and the findings were normal. In all patients, the infarct involved the region that was transiently affected previously.

Four patients (cases 3, 5, 10 and 12) had fatal hemorrhages. One patient (case 3) had an intracerebral hemorrhage in the hemisphere.
that was the site seven days previously of a transient attack. One patient (case 5) had an intracerebral (possibly pontine) or subarachnoid hemorrhage (site unknown); he had had several attacks that were very likely in the region of the vertebral-basilar arterial system approximately one year previously. One patient (case 10) died of an intracerebral hemorrhage on the right side. The day before, the presumed site had caused a left hemiparesis that was present on awakening and persisted; two weeks before he had a transient attack involving the left (opposite) hemisphere. One patient (case 12) died of a cerebral hemorrhage (site unknown) one week after the occurrence of a presumed cerebral infarct in the region previously involved by transient attacks. Of those with hemorrhage, two patients (cases 5 and 10) had grossly bloody spinal fluid and one patient (case 12) had a slightly yellow fluid.

Anticoagulants were used at various times in four patients (cases 1, 9, 11 and 12). In two (cases 1 and 9), the anticoagulants were used during temporary surgical extracorporeal circulation; both patients had transient attacks when not receiving the medicine; both patients died many months later, and postmortem examination showed no significant lesions of the brain or arteries. One patient (case 11) had a transient attack while using anticoagulant medication (degree of effect unknown) and another transient attack about 10 days after use of this medicine was stopped; one day later, she suffered a cerebral infarct. One patient (case 12) was given warfarin a day after two transient and one permanent attacks, but use of the drug was discontinued after two days, and the prothrombin time presumably became normal. One week later, she had a cerebral hemorrhage (site unknown).

Three patients (cases 3, 5 and 10), all of whom died of intracranial hemorrhage, had not received anticoagulant therapy.

From these data, the question concerning the risks of anticoagulant therapy in patients with subacute bacterial endocarditis cannot be answered with certainty. However, the data do indicate that such therapy does not always immediately produce a hemorrhage and that hemorrhages may well occur in subacute bacterial endocarditis without anticoagulant therapy.

Of interest to us was that in six patients (cases 4, 5, 7, 10, 11 and 12) the transient attack was the primary reason, or at least one of the reasons, that patients sought medical attention.

Almost half of the patients had attacks prior to institution of antimicrobial therapy, almost half had them after the institution of such therapy, and a few had attacks both before and after. Several patients had attacks after cultures were found to be normal and antimicrobial therapy had been discontinued.

It must be emphasized as an important diagnostic point that these transient cerebral ischemic attacks associated with subarachnoid bacterial endocarditis did not occur in any patient who was otherwise well, even excluding cardiac murmurs. Definite historical information, appropriate laboratory studies (including multiple blood cultures when necessary), and pertinent examinations will lead to the correct diagnosis and proper therapy.
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