

Refer to: Openshaw H: Neurological complications of endocarditis in persons taking drugs intravenously. West J Med 124: 276-281, Apr 1976

Neurological Complications of Endocarditis in Persons Taking Drugs Intravenously

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A study was made of 46 cases of endocarditis in persons known to take drugs intravenously. Findings included significantly lower ages for those patients in whom infections were right-sided. The neurological complication rate was 39 percent overall and 58 percent in the left-sided group. Neurological complications are unusual in right-sided infection. In about a third of those with neurological complications there were sensorial changes without focal signs. Despite a high mortality, neurological complications in Group D streptococcal endocarditis were relatively infrequent. One case is presented in which a foreign body may have contributed to the formation of the embolic material. The clinical and neuropathological features encountered are compared with those reported in persons with endocarditis who were not addicts. The review indicates that neurological complications in nonaddicts and in addicts are similar in type but are more common and severe in addicts.

INFECTIOUS ENDOCARDITIS in persons using drugs intravenously has come to be a well-recognized clinical problem in most city hospitals. The high mortality and high morbidity noted in reviews¹⁻⁴ published between 1967 and 1970 have been attributed in part to a bias created by reporting particularly severe cases or by using autopsy records

as a source of some cases.⁴ More recent series have noted fewer fungal and Gram-negative cases,⁵ a higher percentage of right-sided infection⁶ and a more favorable prognosis.⁷

The present report concerns the neurological complications seen in drug-related endocarditis from 1966 to 1972 in a city hospital, a university hospital and a Veterans Administration hospital in San Francisco. Including all of the cases filed in the medical record departments in which the diagnoses were clinically and bacteriologically

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Submitted August 25, 1975.

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NEUROLOGICAL COMPLICATIONS OF ENDOCARDITIS

TABLE 1.—Organism, Number of Complications and Mortality in 46 Cases of Endocarditis in Drug Addicts

Organism	Neurological Complications	Mortality
<i>Right-sided</i>		
Staphylococcus aureus ..	14	0
Serratia marcescens	1	1
<i>Left-sided</i>		
Group D Streptococcus ..	9	4
Viridans Streptococcus ..	9	2
Candida albicans	8	3
Staphylococcus aureus ..	5	2
Serratia marcescens	4	4
Microaerophilic streptococcus	1	1
Pseudomonas aeruginosa.	1	1
Mixed	6	3

TABLE 2.—Clinical Presentation of Patients with Neurological Signs

	Cases	Mortality
Focal hemisphere signs with or without sensorium changes	9	5
Sensorium changes alone ("meningoencephalitis")	5	3
Brain stem sign of transtentorial herniation	2	2

TABLE 3.—Types of Neurological Complications

	Number	Mortality
Single infarct	6	3
Multiple infarcts	4	3
Mycotic aneurysm (ruptured)	2	1
Microabscess	1	1
Microabscess and a single infarct	1	1
Abscesses, infarct, mycotic aneurysm ..	2	2

confirmed, the results of this study are closer to those of the earlier reports than to the later series in that the morbidity and mortality were high, and Gram-negative and fungal organisms were encountered relatively frequently. The incidence and types of neurological complications are compared with those reported in recent reviews of neurological complications of endocarditis in nonaddicts.⁸⁻¹⁰ The results are combined when possible with information supplied by recent series of endocarditis cases in addicts.⁴⁻⁷ Case material before 1967 has been covered in reviews, and individual earlier references can be obtained from these reviews.¹⁻³

Results

In all, 46 cases of endocarditis were seen in 41 drug users in the seven-year period. Table 1 outlines the organisms, sites of infection, mortality and incidence of neurological complications in these cases.

The endocarditis was exclusively right-sided in 15 cases, left-sided in 29 cases and bilateral in 2 cases. The age of 26.2 ± 1.2 years (mean \pm SEM) of those with right-sided involvement was significantly lower than that of those patients with left-sided involvement (35.3 ± 1.8). The sex ratio was about one to one in the right-sided group, but the ratio of men to women was nearly six to one in the left-sided group. The pulmonic valve was not involved in any of these cases. Of the left-sided cases, the aortic valve was involved in 17 cases, the mitral in 12 cases and both valves in 2 cases. The overall mortality in the 41 patients was 37 percent. Of those with left-sided infection, the mortality was 54 percent.

Neurological complications were present in 16 patients. This constitutes 39 percent of the entire group and 58 percent of the left-sided group. The average age of 33.6 years was similar to the average age of the left-sided group. The mortality of 69 percent was higher than the mortality of the entire left-sided group. The male preponderance of 15 to 1 was also greater. The endocarditis was confined to the mitral valve in six, aortic valve in five and tricuspid in one. The tricuspid and aortic valves were involved together in three cases, and the mitral and aortic valves were involved together in one case.

Tables 2 and 3 summarize the clinical and pathological findings in these 16 cases with neurological complications. Postmortem examination of the brain was done in all of the 11 fatal cases. Five patients had changes in sensorium (from "mildly confused" to "obtunded"), meningismus and pleocytosis (from 5 to 313 cells), but no focal neurological signs. In all of the three fatal cases in this nonfocal group, cerebral microabscesses were noted on postmortem examination. There was an associated silent frontal infarct in one of these cases, and a mycotic aneurysm and septic emboli in a second. The two surviving patients in the nonfocal group had a similar clinical presentation with headache, dulled mentation, nuchal rigidity, pleocytosis of 9 and 37 cells, and sterile spinal fluid. In one of these cases, a small left frontal and occipital blood-brain-barrier defect was found on an initial brain scan. In the other patient, there was a diffusely slow electroencephalogram (EEG) and a normal, early brain scan.

In nine patients there were focal hemispheric signs with or without sensorial changes. The deficits included hemiplegia in six patients, an iso-

lated visual field defect in one, a fluent aphasia in one and mild nondominant parietal lobe signs in one. The cause of the focal findings was an infarct in six patients, a ruptured mycotic aneurysm in one and an abscess in one. In this last patient there were diffuse signs of meningoencephalitis including a pleocytosis of 14 cells for one week before a right hemiplegia developed. In all the other patients of this group, there was a rather abrupt onset of the neurological deficit.

Two patients presented with sensorial changes and rapidly developing brain stem signs of tentorial herniation without known antecedent hemispheric signs. On postmortem examination, multiple cerebral emboli and edema were noted in one and a ruptured mycotic aneurysm with intraventricular bleeding in the other. Endocarditis was not diagnosed before death in either of these patients.

There were four cases of mycotic aneurysms. The associated organisms included *Serratia marcescens*, viridans *Streptococcus* and *Staphylococcus aureus* (two cases). In two of these patients there was an angiographically verified extracranial mycotic aneurysm on the celiac trunk and the descending aorta. A massive subarachnoid hemorrhage occurred in two of the four patients. One of these patients survived with only a subtle neurological deficit. In the other two patients, unruptured mycotic aneurysms were seen at autopsy.

Diffuse microabscesses were seen in four postmortem examinations. *Serratia marcescens* was the causative organism in three cases and *Staphylococcus aureus* in one case. There were associated infarcts or mycotic aneurysm in all but one of these cases. Only one large abscess was seen in all of the patients. In this case, *Staphylococcus aureus* infection was present with associated cerebral infarct and unruptured cerebral mycotic aneurysm.

One pathologically studied case was unusual because of the presence of cotton fibrils in the right atrial wall. In this patient there was a viridans *Streptococcus* infection of the mitral and aortic valves. Foreign body giant cells were present in the right atrium, the aortic valve leaflet and the left cerebral hemisphere adjacent to a large hemorrhagic infarct.

Reports of Cases

In three cases, patients with endocarditis presented predominantly with neurological symptoms and signs. One patient was confined to a state

psychiatric hospital because of confusion and paranoid hallucinations. Findings in later examinations showed an aortic murmur, fluent aphasia and mild right hemiparesis. Blood cultures grew a candida organism. The spinal fluid contained 12 leukocytes. An EEG showed a left-sided low amplitude slow wave focus. The brain scan was normal. After an aortic valve replacement, the infection was controlled with administration of amphotericin. The neurological deficit remained unchanged without further elucidation, and the patient was lost to follow-up.

A second patient was brought to the emergency room following an automobile accident. There were no signs of head injury. However, during the next three hours, the sensorium changed from lethargy to coma, and a left hemiparesis and a right third nerve palsy appeared. Emergency burr holes revealed a blue-black brain on the right and subarachnoid but no subdural blood. An arteriogram was then obtained which showed an aneurysmal dilatation of the proximal right middle cerebral artery. Later an alpha-hemolytic streptococcal organism was cultured from the blood. The patient was successfully treated with decadron, mannitol and antibiotics. Another arteriogram made several weeks later failed to show the aneurysm. Months after the insult, the only deficit was mild spasticity on the left. Although a cerebral contusion was initially suspected, the arteriogram and subsequent course suggest that a ruptured mycotic aneurysm produced this neurological situation.

A third patient presenting with neurological symptoms and signs was brought to the emergency room in a semicomatose state, became decerebrate and deeply comatose in twelve hours, and finally herniated despite therapy with osmotic agents. The scanty available history indicated that fever and malaise had been present for two weeks and headache and confusion for 12 hours. On the initial examination a mitral murmur and depressed sensorium were noted, but no focal neurological signs. The spinal fluid contained 313 leukocytes (90 percent neutrophils), 495 red cells, protein of 108 mg per 100 ml and glucose of 44 mg per 100 ml. Cerebral arteriography showed multiple blocked vessels. After death, the blood cultures grew a microaerophilic streptococcus, but the spinal fluid culture was sterile. On postmortem examination, multiple emboli were noted without evidence of mycotic aneurysm or abscess formation.

Comment*Frequency of Neurological Complications*

In discussing the frequency of neurological and other complications of endocarditis in addicts, left-sided and right-sided endocarditis should be considered separately. Sole right-sided infection has been reported in 9 percent⁴ to 72 percent⁶ of series of endocarditis in addicts. Tricuspid infection accounted for about a third of the patients in the present study. Pulmonary embolism is the hallmark of tricuspid endocarditis;^{1,2} peripheral embolic signs appear less frequently than in left-sided endocarditis^{6,7} and the mortality is some two to five times less.^{1,2,6} With the present data in a combined series of 165 patients,^{1,2,6,7} it would appear that addicts with right-sided infections tend to be younger than those with left-sided infections (29.7 ± 0.88 compared with 36.2 ± 1.28). Moreover, in only five of 93 cases of tricuspid endocarditis from a combined series was there an infection with an organism other than *Staphylococcus aureus*.^{2,6,7}

Neurological complications occur only occasionally in isolated right-sided infections. Ramsey and co-workers noted only one case in 28 addicts with tricuspid endocarditis reported in the literature before 1970.² One of 15 cases reviewed was noted in the present series.

If one considers only left-sided endocarditis in addicts, the chances of major neurological complications are greater than the 12 percent¹⁰ to 29 percent⁸ of nonaddicts with endocarditis. In Louria's review of earlier case reports, there were cerebral emboli in 45 percent of 20 published cases in which sufficient clinical information was given.¹ The present study reports a complication rate of 58 percent. The mortality of 69 percent in these patients is close to the mortality of 63 percent reported by Jones in nonaddicts with endocarditis having major neurological complication (excluding the miscellaneous complications of headache, mononeuritis and convulsions).⁸

The higher complication rate in addicts may in part be secondary to the failure of some to undergo a full antibiotic course. Follow-up medical care is often neglected, and many addicts resume their drug habit. Two and three separate bouts of endocarditis were seen in three addicts in this series.

Probably more important in determining the complication rate is the heightened virulence of

the organisms seen in the addict population. The five cases of *Serratia marcescens* endocarditis in the present series were all associated with neurological sequelae and were all fatal. Fungal endocarditis accounted for 17 percent of the cases reviewed here. Although an identical percentage was noted in an earlier review,¹⁴ most recent series report a much lower incidence.^{2,5,6} Twenty percent of the patients in the present series were infected with a Group D streptococcal organism. In recent surveys, only six cases of enterococcus were present in a total of 123 cases of endocarditis.^{1,2,4-7} Combining these six cases with the nine in the present series, the neurological complication rate was only one case in the 15 despite a mortality of 40 percent in these patients. More data clearly must be gathered before it can be determined if the embolic potential of enterococcal endocarditis is less than that of Gram-negative, *Staphylococcus aureus* or fungal endocarditis.

The case in which cotton fibrils were present in the heart raises the question whether foreign bodies introduced by venipuncture can affect the course of endocarditis in addicts. Foreign body granulomata unassociated with endocarditis have been reported in the lung,^{11,12} liver,¹³ and the spleen and kidney.¹⁴ Surgical placement of foreign bodies in the heart apparently increases the risk of endocarditis.¹⁵⁻¹⁸ One could speculate that in unusual cases, talc or cotton fibril contamination could make endocarditis more likely to occur, the infection more resistant to treatment or the embolization potential of the lesion greater.

Types of Neuropathological Lesions

With the possible exception of a delayed endarteritis,¹⁹ all the neuropathological complications of endocarditis appear to result from either septic or nonseptic emboli. Critical factors that may determine whether a septic embolus results in a simple infarct, a mycotic aneurysm or an abscess include the site in which the embolus lodges, the virulence of the organism and the defenses of the host (including the adequacy of antibacterial therapy). The associations of abscess and infarcts in three cases and abscess, infarcts and mycotic aneurysm in two cases show that different pathological processes may be simultaneously present.

The most common neuropathological complication in this and other series of endocarditis^{8,9} is embolic infarction without abscess or aneurysmal

formation. In 29 percent of the left-sided infections such simple infarcts, either single or multiple, were present. This can be compared with 12 percent in Jones' series of 385 nonaddict patients with endocarditis.⁸

Mycotic aneurysms were shown angiographically or pathologically in a fourth of those cases with neurological sequelae. This corresponds to 13 percent of the cases of left-sided endocarditis, a slightly higher incidence than the 2 to 9 percent from Ziment's review.⁹

Katz and associates have recently shown angiographically the development of a mycotic aneurysm in an endocarditis patient with a clinical infarct.²⁰ In this case, a segmental vascular occlusion by a septic embolus apparently resulted in an initial infarct and delayed aneurysmal formation. If arteriography would be used more frequently in this situation, the incidence of recognized aneurysms would probably be greater than the 2 to 9 percent reported. The patients in the present series in whom a mycotic aneurysm was diagnosed before death presented with an abrupt subarachnoid hemorrhage without a history of a preceding infarct. Presumably in this type of patient, the septic embolus involves primarily the vasa vasorum; or because of collateral flow, there is no clinical infarct despite a segmental vascular occlusion by the septic embolus.

Although organisms of low virulence are said to be most often associated with mycotic aneurysms,⁹ *Serratia marcescens* and *Staphylococcus aureus* were isolated in three of the four cases reported here. Two additional cases of mycotic aneurysm in addicts also recently reported virulent organisms.²¹ In both of these cases and in two of the cases reported here (*Staphylococcus aureus* and a viridans *Streptococcus* infection), there was an abrupt hemorrhage when the patient either was receiving no therapy or therapy with an antibiotic that was later shown to be ineffective *in vitro* against the organism. These cases tend to lend clinical support to the hypothesis discussed by Molinari and co-workers.²² In their experimental model of mycotic aneurysms in dogs, bleeding tended to occur when no antibiotics were given; whereas, with antibiotic therapy, the aneurysms were unruptured and abscesses were seen.

The four cases of microabscesses reported here were in patients with virulent organisms who were treated from 12 days (*Staphylococcus aureus*) to more than a month (three cases of

Serratia marcescens). Two of these four cases had associated unruptured mycotic aneurysm. The 13 percent incidence of abscesses in this series is high compared with that in most series of even acute endocarditis in the antibiotic era.⁹

Clinical Features

The main neurological diagnostic difficulty in endocarditis is the patient who presents not with focal signs but with an alteration in sensorium, often with signs of meningeal irritation. Recent reviews have emphasized the relatively common and serious nature of such "toxic psychosis" or "toxic confusional state."^{8,9}

Including only those cases in which there were objective laboratory or clinical signs of neurological abnormality, 19 percent of the patients with left-sided endocarditis qualified as having primarily a toxic encephalopathy. This corresponds to a third of those patients with neurological complications. Underlying "silent" infarcts, abscesses and mycotic aneurysms were shown to be present in those cases that came to postmortem examination. Jones reports an overall incidence of "toxic psychosis" of 7 percent or about a third of those with major neurological complications.⁸ The mortality of 64 percent reported by Jones is similar to the 66 percent mortality found in the present series. The mortality in the addict endocarditis patients with neurological complications is essentially the same in the group with focal signs and in those who have "toxic psychosis" without focal features.

These clinical features may be especially difficult to recognize in an addict because of the high frequency of infections in addicts, the problem of drug withdrawal, a baseline personality disorder in some, and a secretiveness and suspicion shown by many of these patients when they are isolated in medical surroundings.

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NEUROLOGICAL COMPLICATIONS OF ENDOCARDITIS

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