Incidence of Strokes and Its Prognosis in Patients on Maintenance Hemodialysis

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SUMMARY

The incidences of cerebral hemorrhage (CH), cerebral infarction (CI) and subarachnoid hemorrhage (SAH) were examined retrospectively in patients with chronic renal failure on maintenance hemodialysis, followed for 13 years in our 26 satellite dialysis centers. During 10,364 patient-years of experience (PYE), CH developed in 66, CI in 16, SAH in 3 and unclassified stroke in 5 cases. The incidence was 637 per 10^5 PYE for CH and 154 for CI, the former being approximately 5 times and the latter one third of the incidence of CH or CI in the general population in Japan. Forty-six percent of fatal CH cases died within 24 hours and 73% within 3 days after the onset, while 13% of CI deaths died within 24 hours and 26% within 3 days. These data suggest that factors such as the regular use of heparin as an anticoagulant in hemodialysis patients or other inherent factors in these patients may increase vulnerability to CH and decrease the probability of CI.

Additional Indexing Words:

Cerebral hemorrhage Cerebral infarction Subarachnoid hemorrhage Endstage renal failure Cerebrovascular accident

SINCE regular maintenance hemodialysis for renal failure was introduced in 1960, intracranial hemorrhage has been recognized as one important complication. Subdural hematoma in hemodialysis patients was reported first in 1969 by Leonard et al¹⁾ and subsequently intracerebral and subarachnoid hemorrhages were noted by many investigators.²⁾⁻⁵⁾ Patients

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aged 35 to 54, who underwent hemodialysis and kidney transplantation, died 50 times more frequently than did the general population of France in 1978.²⁾ Cerebral hemorrhage(CH), subarachnoid hemorrhage(SAH) and cerebral infarction(CI) are not uncommon in these hemodialysis patients. Annual death rates from cerebrovascular accidents in these patients were reported as 13.7% in Europe in 1978²⁾ and 14.2% in Japan in 1983.³⁾ During 5 years of treatment with maintenance hemodialysis, Siddiqui et al⁴⁾ found that 4 patients died from intracranial hemorrhage among 41 in the sample. A prospective study of 1,453 chronic hemodialysis patients in 33 French dialysis centers between 1972 and 1978 demonstrated that 198 cases died during the follow-up period, of which 35 cases or 17.7% died from strokes.⁵⁾ Given recent increases in the number of the patients who are introduced into maintenance hemodialysis, it is important to assess the incidence of stroke and its prognosis during prolonged treatment. This paper investigates the incidence of strokes in a large number of maintenance hemodialysis patients in order to form a basis for assessing risk factors affecting the development of strokes.

PATIENTS AND METHODS

The study population consisted of patients treated with maintenance hemodialysis from December 1971 to December 1984 in our 26 satellite dialysis centers. The numbers of patients who were maintained at the end of December in each dialysis center were tabulated for each year and the study comprises a total of 10,364 patient-years of experiences (PYE) over the period 1971–1984. The development of strokes was examined retrospectively in this patient pool. CH, CI and SAH were included as strokes but a transient ischemic attack or hypertensive encephalopathy was excluded. The diagnosis of stroke was made clinically with the aid of CT scans and lumbar puncture. Autopsy data confirmed the diagnosis in some cases. An unclassified stroke was registered as cerebrovascular disease (CVD). When the patients died within 6 months of the onset of strokes, without an other major cause of death, they were listed as stroke death. There were 7 cases of CH and 2 cases of CI where the exact time interval from the last hemodialysis treatment to the onset of stroke was not determined because of incomplete records. The time of onset of a stroke was unclear in 1 case of CVD.

Hemodialysis was performed 3 times per week in 5 to 6 hour sessions, using a subcutaneous arterio-venous fistula. There were no differences in the settings for dry weight, levels of uremia and antihypertensive treatment in the centers covered by the study. Data were expressed as mean $\pm$ SD and

calculated by one-way analysis of variance prior to an unpaired Student's t-test. The Chi-square test was also used for statistical analysis. P values less than 5% were considered to be significant.

RESULTS

Among 10,364 PYE, there were 90 cases of strokes (66 with CH, 16 with CI, 3 with SAH and 5 with CVD). Patient profiles of these cases are listed in Table I. CH comprised 73% of all the strokes and CI comprised 18%. The average age of the patients did not differ between CH(53 yrs) and CI (59 yrs), but it was significantly higher in CH($p < 0.05$) and CI($p < 0.01$) than in SAH(38 yrs). The duration of hemodialysis treatment prior to strokes ranged from 18 to 61 months, but the differences were not statistically significant among the groups of patients. Fifty-five of 66 CH cases and 8 of 16 CI cases died from the stroke, and all 3 SAH and 4 of 5 CVD cases were fatal as well.

The incidence of strokes per 10^5 PYE is shown in Table II. The incidence of CH was 637 per 10^5 PYE, being 4 times greater than the incidence of CI (154). By contrast, the incidence of SAH was very low (29).

The time interval from the end of the last hemodialysis session to the

Table I. Sex, Age and Duration of Hemodialysis (HD) in Maintenance
HD Patients Who Developed Stroke

Type of stroke	No of cases	Sex		Age (yrs)	Duration of HD (mos) prior to stroke	No of deaths
		male	female			
CH	66	43	23	$53 \pm 11^{**}$	40 ± 45	55 (83%)
CI	16	10	6	$59 \pm 12^*$	23 ± 27	8 (50%)
SAH	3	2	1	38 ± 9	61 ± 22	3 (100%)
CVD	5	3	2	55 ± 8	18 ± 20	4 (80%)
	90	58	32	53 ± 12	39 ± 41	70

CH=cerebral hemorrhage; CI=cerebral infarction; SAH=subarachnoid hemorrhage; CVD=unspecified stroke. Values are mean $\pm$ SD.

* $p < 0.05$, ** 0.01 (vs SAH).

Table II. Annual Incidence of Strokes per 100,000 Patient-years of Experience

Type of stroke	Incidence
CH	637
CI	154
SAH	29
CVD	48

Table III. Time Interval from the End of the Last Hemodialysis (HD) to the Onset of Stroke

Type of stroke	No of cases	Time interval (hrs)	During or within 6 hrs after HD	6 hrs or more after HD
CH all	59	21±27	23 (39%)	36 (61%)
survived	10	24±19	3 (15%)	7 (19%)
died	49	21±23	20 (85%)	29 (81%)
CI all	14	11±21	9 (64%)	5 (36%)
survived	7	2±5*	6 (67%)	1 (20%)
died	7	25±26	3 (23%)	4 (80%)

Strokes developed during HD were calculated as 0 hour.

Values are mean±SD.

* $p<0.05$ vs cases died in CI. Seven cases in CH and 2 in CI were excluded because the exact time of the last HD was undetermined.

Table IV. Length of Survival (hrs) of the Death Cases Following Strokes

Type of stroke	No of cases	Length of survival	Range
CH	55	72±128	2-720
CI	8	436±1151	22-3600
SAH	3	120±70	19-192
GVD	3	96±115	109-288

Values are mean±SD. One case in CVD was excluded because the exact time of onset was undetermined.

onset of stroke is shown in Table III. When the stroke developed during hemodialysis, the interval was designated 0 hour. Average values for the time interval were 21 hours for CH and 11 hours for CI, respectively; the difference was not significant. However, the time interval was significantly shorter in CI cases who survived than in those who died from the attack within 6 months ($p<0.05$). Strokes developed during or within 6 hours of the previous hemodialysis session in 39% of 59 CH cases, and 64% of 14 CI cases. The remaining CH and CI had attacks at least 6 hours after the session. Twenty of 23 CH cases that were manifest within 6 hours of dialysis were fatal (87%), while 6 of 9 cases with CI survived (67%). By contrast, 7 of 36 CH cases that had developed at least 6 hours after dialysis survived for more than 6 months, while 4 of 5 cases with CI died within 6 months.

The average survival period of the patients who died within 6 months after stroke is shown in Table IV. The survival time was 72±128 (SD) hours for 55 CH cases and 436±1151 hours for 8 CI cases, respectively (not significant). As tabulated in Table V, 46% of CH patients died within 24 hours after the onset and, cumulatively 73% were dead within 3 days and

Table V. Distribution of the Time Intervals from the Stroke-onset to Death in the Fatal Cases

Type of stroke	Died after the onset (day)			
	<1	1-3	3-30	30<
CH	25 (46%)	15 (27%)	15 (27%)	0 (0%)
CI	1 (13%)	1 (13%)	4 (50%)	2* (24%)

 $\chi^2=17.4$. $p<0.01$.

* 2 cases died at 60 and 150 days, respectively.

100% within 1 month of hemorrhage. By contrast, 13% of the CI patients died within 24 hours, 26% within 3 days and 76% within 1 month. This difference in survival time between CH and CI patients was significant by a Chi-square test ($p<0.01$), indicating that CH patient died much earlier than CI patients.

DISCUSSION

The incidence of strokes has not yet been reported in a large number of maintenance hemodialysis patients. However the present results can be compared with the data obtained by field surveys in epidemiological studies. Robins and Baum,⁶⁾ who summarized previous reports in the literature, stated that the incidence of CH in the U.S.A. and Europe ranged between 17 to 88 per 10^5 PYE. On the other hand, in the Japanese general population, the incidence has been reported to be 120⁷⁾ or 212⁸⁾ per 10^5 PYE in the 1970s. Thus, the incidence of CH in hemodialysis patients was 3 to 5 times higher than the incidence in the general population, indicating that this class of patients is at greater risk.

Possible causative factors for intracranial hemorrhages in these patients include hypertension, systemic heparinization, ultrafiltration to treat fluid accumulation, poor platelet adhesion and vascular access infection^{9),10)}; the potential roles of hypertension and anticoagulant have been especially emphasized. According to our previous report, 58% of maintenance hemodialysis patients were hypertensive,¹¹⁾ while the present study found that 66.7% of hemodialysis patients with CH had hypertension. Recent advances in the treatment of hypertension may decrease the death rate from stroke in the first 6 months of dialysis into a tenth of the figure in the mid-1960s.⁹⁾ However, a majority of the hemodialysis patients still have hypertension, which may be partly responsible for a higher incidence of CH in hemodialysis patients.

In regular hemodialysis a high dose of heparin is given 3 times a week,

4 to 5 hours each during hemodialysis. The anticoagulant effects of heparin persist for 6 hours after administration. Siddiqui et al⁴⁾ have reported a prolonged clotting time as a causative factor of death in 3 out of 4 cases of intracranial hemorrhage. Even in the absence of hemodialysis, 31% of the sudden deaths from CH were found to be on long-term oral anticoagulant therapy.¹²⁾ However, the shorter survival time suggests that CH in hemodialysis patients is clinically more severe. In fact, CT scans from this group of patients demonstrated large hematoma in the cerebral hemispheres or in the brain stem.¹³⁾ Systemic heparinization seems to be an important factor in the poor prognosis of these patients.

According to epidemiological studies in Japan, the incidence of CI was 470⁷⁾ or 586⁸⁾ per 10⁵ PYE, whereas it was 154 per 10⁵ PYE in hemodialysis patients. Thus, there is a major difference in the incidence of CH and CI in hemodialysis patients and the general population, with a higher incidence of CH and a lower incidence of CI in these patients. It is suggested that heparinization, rather than hypertension plays a more important role in either the development of CH or the prevention of CI in the hemodialysis patients. In the present study, all cases of SAH died but the small sample size precludes further analysis of the data. Thus, further studies of this less common group of patients are needed to determine possible risk factors for SAH as a function of hemodialysis.

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