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PATHOPHYSIOLOGY OF REVERSIBLE SUDDEN DEAFNESS — EPIDEMIOLOGICAL STUDY —

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Abstract. Many aspects of the etiology and pathophysiology of reversible sudden deafness remain obscure. In order to better understand the pathophysiology of reversible sudden deafness we compared the results of two therapies which have different mechanisms of action. The results of therapy with tranexamic acid alone in 49 cases (57 ears) of sudden deafness were compared with the results of treatment with so-called antisludging agents in 65 cases (69 ears) using the chi square contingency test. The same therapeutic effect was observed in both groups despite the different modes of chemical action of the two therapeutics. A series of processes involving an increase in permeability of vascular walls and related edema, and extravascular red cell oozing due to hypoxia or anoxia leading to tissue damage in the inner ear seem to be important factors in the etiology and pathophysiology of reversible sudden deafness.

Key words: sudden deafness, pathophysiology, epidemiological study, therapeutic effects.

Histopathological findings of idiopathic irreversible sensory neural hearing loss have been reported by several authors (1-6). According to these histopathological studies, sudden deafness has been reported to be of viral, vascular, neural and endolymphatic hydroptical origins. Among these causes, viral labyrinthitis reported by Schuknecht *et al.* (1, 2) is held to be the most likely etiology.

On the other hand, many authors have suggested that the pathophysiology of reversible sudden deafness is due to vascular disturbances such as spasm, sludging and thrombosis in the cochlea (7-15).

We thought that the pathophysiology of reversible sudden deafness could be studied by comparing the results of two therapies which have different mechanisms of action.

The criteria of diagnosis and hearing recovery from sudden deafness were based upon standards set by the Sudden Deafness Research Committee of Japan.

MATERIALS AND METHODS

Dianogstic criteria of sudden deafness. Sudden deafness was designated as a specific disease by the Ministry of Health and Welfare of Japan in April 1973, and research into the epide-

miology, etiology, treatment and prevention of sudden deafness was started on a nationwide scale. The diagnostic criteria of sudden deafness were defined by the Sudden Deafness Research Committee of Japan in July 1973 as follows:

Main symptoms. 1. Suddenly occurring deafness: Patient is able to state clearly when he noticed deafness. 2. Idiopathic deafness (including uncertain cases): All cases that have no clear etiology for sudden deafness, including cases that involve a slight cold at or shortly before the time of onset. 3. Profound perceptive deafness: A) Perceptive deafness is not necessarily profound though deafness could not actually be noticed in many cases if the deafness were not profound. B) It is not discovered by recruitment. C) Recovery and/or worsening of hearing acuity is not cyclic. D) In many cases, deafness is unilateral but in a few cases deafness is bilateral concurrently.

Accessory symptoms. 1. Tinnitus: Tinnitus is noticed mostly just before or after deafness occurs. 2. Dizziness, nausea and vomiting: Dizziness, which may be accompanied by nausea and vomiting, is occasionally noticed before or after deafness occurs but is not repeated. 3. Symptoms from other cranial nerves are absent.

Subjects. The subjects in this study were 114 patients (126 ears) seen in Ear Nose and Throat Clinics, Hiroshima Citizen's Hospital, Hiroshima, Japan, Kobe Nishi-shimin Hospital, Kobe, Japan and Okayama Red Cross General Hospital, Okayama, Japan from January 1965 to August 1976. Of these, 49 patients (57 ears) were treated with tranexamic acid* (16) and 65 patients (69 ears) were treated with so-called antisludging agents**.

Working hypothesis. The working hypothesis used in this article is shown schematically in Fig. 1. Two sampling groups, A and B, which were randomly selected from a homogenous population, were treated with two types of therapeutics having different mechanisms. If the same therapeutic effect were obtained in both groups then, we thought that the existence of a

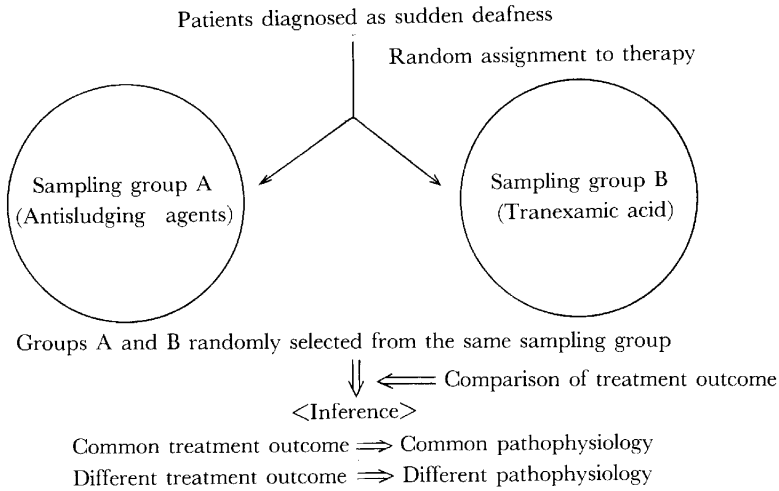

Fig. 1. Working hypothesis

* : Transamin^{R}, Daiichi Seiyaku Co., Ltd. Tokyo, JAPAN

**: Low molecular-weight dextran, steroids, 7 % $NaHCO_3$ solution, 0.1 % novocaine, vasodilators, or adenosine triphosphate (ATP).

pathophysiology commonly receptive to the two treatments could be inferred.

Comparison of treatments and groups. The chi square contingency test was used in this paper to compare the outcomes of the two treatments and the characteristics of the two sampling groups.

Standards of hearing recovery. Standards of hearing recovery were defined by the Sudden Deafness Research Committee of Japan in October 1974 and have been previously described (15); in this paper, they are summarized as follows:

Healed: 1. Recovery within 20 dB at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. 2. When the diseased ear recovered to the same auditory state as the healthy ear, and hearing acuity in the healthy ear was stable.

Remarkably recovered: Cases in whom the arithmetical mean hearing loss at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz recovered by 30 dB or more.

Slightly recovered: Cases in whom the arithmetical mean hearing loss above 5 cycles recovered by 10 to 30 dB.

Unchanged (including worsening): Cases in whom the arithmetical mean hearing loss above 5 cycles was limited to $\pm$ 10 dB.

RESULTS

Comparison of the two groups. For the purpose of comparing the two therapy groups, factors were selected from data that were obtained at the time of the first medical examination. These included sex, age, season at onset, affected side, the time from onset to the first medical examination, the degree of hearing loss at 500 Hz and 4000 Hz, the existence of dizziness, and the shape of the initial audiogram.

When factors of the two treatment groups were compared by the chi square contingency test, the differences were not statistically significant at a P value of

TABLE 1. DISTRIBUTION BY EACH FACTOR OF PATIENTS TREATED BY TWO THERAPIES

Factors	Therapy groups	
	T. A.[a]	A. S. A.[b]
Sex		
Male	22 (44.9 %)	28 (43.1 %)
Female	27 (55.1 %)	37 (56.9 %)
Total of patients	49	65
Age		
5 - 14	2 (4.1 %)	5 (7.7 %)
15 - 24	4 (8.2 %)	9 (13.8 %)
25 - 34	6 (12.2 %)	9 (13.8 %)
35 - 54	23 (46.9 %)	28 (43.1 %)
$\geqslant$ 55	14 (28.6 %)	14 (21.6 %)
Total of patients	49	65
Season at onset		
Spring	17 (34.7 %)	16 (24.6 %)
Summer	8 (16.3 %)	22 (33.9 %)

TABLE 1. continued

Factors	Therapy groups	
	T. A.[a]	A. S. A.[b]
Autumn	5 (10.2 %)	11 (16.9 %)
Winter	19 (38.8 %)	16 (24.6 %)
Total of patients	49	65
Affected side		
Unilateral		
Right	20 (40.8 %)	27 (41.5 %)
Left	21 (42.9%)	34 (52.3 %)
Bilateral	8 (16.3 %)	4 (6.2 %)
Total of patients	49	65
Days from onset to the first medical examination		
0 - 7 days	32 (65.3 %)	39 (60.0 %)
8 - 14 days	5 (10.2 %)	17 (26.2 %)
⩾ 15 days	12 (24.5 %)	9 (13.8 %)
Total of patients	49	65
Hearing loss at the first medical examination		
(i) 500 Hz		
⩽ 35 dB	15 (26.3 %)	17 (24.6 %)
40 - 85 dB	37 (64.9 %)	40 (58.0 %)
⩾ 90 dB	5 (8.8 %)	12 (17.4 %)
Total of ears	57	69
(ii) 4000 Hz		
⩽ 35 dB	13 (22.8 %)	16 (23.2 %)
40 - 85 dB	34 (59.7 %)	33 (47.8 %)
⩾ 90 dB	10 (17.5 %)	20 (29.0 %)
Total of ears	57	69
Dizziness		
Present	15 (30.6 %)	25 (39.1 %)
Absent	34 (69.4 %)	39 (60.9 %)
Total of patients	49	64[c]
Shape of the initial audiogram		
Low tone deaf.	5 (8.9 %)	7 (10.2 %)
Flat	13 (23.2 %) → 23 (41.1 %)	19 (27.5 %) → 33 (47.8 %)
Concave	5 (8.9 %)	7 (10.2 %)
Convex	7 (12.5 %)	12 (17.4 %)
High tone deaf.		
gradual	15 (26.9 %) → 33 (58.9 %)	9 (12.9 %) → 36 (52.2 %)
abrupt	6 (10.7 %)	5 (7.3 %)
Total deaf.	5 (8.9 %)	10 (14.5 %)
Total of ears	56[d]	69

a: Tranexamic acid, *b*: Antisludging agents, *c*: Excludes one patient because of no discription on dizziness in the hospital record. *d*: Excludes the dip shape audiogram because of there being only one case in the tranexamic acid group and none in the antisludging agents group.

TABLE 2. DISTRIBUTION OF TREATMENT OUTCOME[a]

Therapy	Healed or remarkably recovered		Slightly recovered		Unchanged		Total No.[b]
	No.[b]	%	No.[b]	%	No.[b]	%	
Tranexamic acid	24	42.1	12	21.1	21	36.8	57
Antisludging agents	37	53.6	12	17.4	20	29.0	69

a: The differences between the two treatment outcomes are not statistically significant($p < 0.05$).
b: Number of ears.

less than 0.05 (Table 1). If these two sampling groups were treated by the same therapy, similar therapeutic effects should be obtained, that is to say, no bias between treatment groups was suggested.

Comparison of the two therapeutic effects. One hundred fourteen sudden deafness patients (126 ears) were divided into two therapy groups. Forty-nine patients (57 ears) were treated with tranexamic acid and 65 patients (69 ears) were treated with so-called antisludging agents. Patients were classified into 3 groups based upon treatment outcome: healed or remarkably recovered, slightly recovered and unchanged or worsened.

As shown in Table 2, when the tranexamic acid treated group was tested against the antisludging agent treated group by the chi square contingency test, the differences were not statistically significant ($p < 0.05$).

DISCUSSION

The etiology of reversible sudden deafness is still obscure as an autopsy has been impossible at an early stage of development. At the present time, however, results can be obtained using various treatments which assume different pathophysiologies of the inner ear in cases of sudden deafness (8, 9, 11, 13, 15, 17-21).

In a clinical investigation of 15 patients, Simmons (22) proposed that very abrupt sorts of hearing losses can be caused by a mechanical defect other than blood vessel rupture or occlusion, namely, by rupture, breaks, or dislocations of intracochlear membranes.

Morimitsu *et al.* (18) recently proposed the latest idea about the pathophysiology of sudden deafness in regard to meglumine diatrizoate treatment. They presumed that sudden hearing loss without vertigo could be due to a breakdown in the blood cochlea barrier in the area of the stria vascularis with a subsequent decrease in the endocochlear DC potential. They suggest that because of the molecular weight and character of meglumine diatrizoate, the broken membrane pores are filled and the sodium pump is activated again to produce normal endolymph.

Treatments having two different mechanisms were used in this study. One

group of 65 patients (69 ears) with sudden deafness was treated with a combination of agents such as low molecular dextran, steroids, vasodilators, ATP, a solution of 7% $NaHCO_3$, novocaine, etc., which function through antisludging action (23-25). The other group of 49 patients (57 ears) were treated only with tranexamic acid which has an antiplasmin action (26). The so-called antisludging agents act on the process of blood coagulation, and as a consequence, the flow of blood may be improved (23), while antiplasmin is an important hemostatic agent which inhibits the acceleration of fibrinolysis (26). There was, however, no statistically significant difference between the therapeutic effects of the two medications having widely different modes of action.

If we speculate upon the inner ear pathophysiology in sudden deafness, on the basis of our hypothesis in this study, we may reasonably propose the following theory. The sludge phenomena (23, 27), having shown itself through the therapeutic effectiveness of the antisludging agents, may exist in the pathophysiology of reversible sudden deafness, and are thought to occur in the steps indicated in Fig. 2. The phenomena of fibrinolysis (28-31), the steps of which are shown in Fig. 3, are also thought to occur in the pathophysiology of reversible sudden deafness because the antiplasmin agent is effective. Therefore, the pathophysiology commonly responding to the differing treatments is suggested as shown in Fig. 4.

Koide *et al.* (32, 33) and Misrahy *et al.* (34) reported in experimental studies

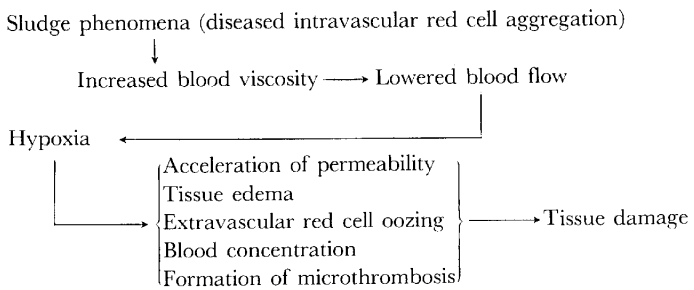

Fig. 2. Pathophysiology related to sludge phenomena (23, 27)

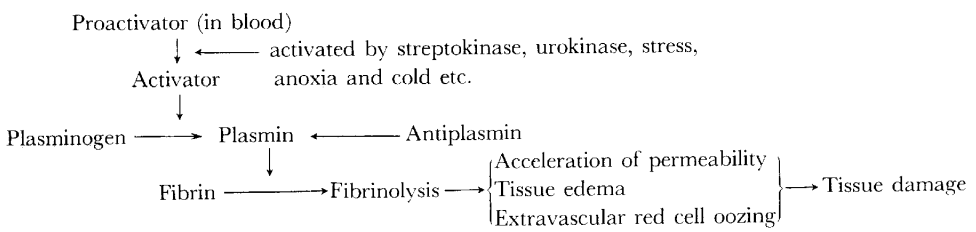

Fig. 3. Fibrinolysis system and it's pathophysiology (28-31)

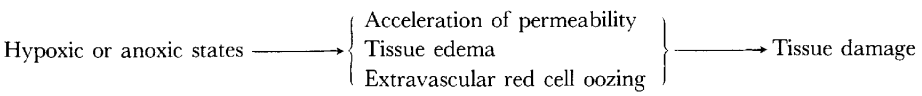

Fig. 4. Common pathophysiology to sludge phenomena and fibrinolysis

that oxygen may play an important part in the action of the inner ear and in the maintenance of inner ear function. Yanagita *et al.* (13) clinically observed that favourable results were obtained by hyperbaric oxygen therapy in sudden deafness patients. They attributed the pathophysiology of sudden deafness to the hypoxia in the inner ear resulting from circulatory disturbances and the subsequent metabolic disruption due to the hypoxia. From these reports, it seems probable that the pathophysiology of the inner ear in the early stages of sudden deafness is due to hypoxia or anoxia.

Kimura and Perlman (35) who experimentally produced a congested vascular lesion in the cochlea through sudden extensive venous obstruction of the inferior cochlear vein, observed the inner ear histologically and reported edema and hemorrhage of the stria vascularis and hemorrhage in the perilymphatic and endolymphatic spaces. Anniko (36) experimentally observed that the morphological changes in the cochlea following administration of ethacrynic acid occurred initially in the stria vascularis of the basal coil as shown by an increased intracellular vesiculation of the marginal cells followed by inter- and intracellular edema in the intermediate cell layer. Accordingly, vascular lesions such as edema and hemorrhage in the cochlea of humans might be involved in the pathology of some cases of sudden deafness of obscure origin. However, hemorrhage into the labyrinth in leukemia is well documented (37).

Based on the results of epidemiological and histopathological studies, hypoxic or anoxic states in the inner ear might occur and then, secondarily, acceleration of vascular permeability in tissue, tissue edema and extravascular red cell oozing may appear in the inner ear leading to hypofunction of the inner ear and consequently to reversible sudden deafness. We also think that this pathophysiology of sudden deafness might occur to some extent in cases of spontaneous recovery (19, 22, 38, 39).

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