Acute Cardiac Death of Unknown Etiology
A Preliminary Report

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Since the Medical Examiner System was established in 1948, more than 100 cases of acute cardiac deaths of unknown etiology have been found annually mainly composed of apparently healthy young males. The majority died during sleep at night and their autopsy findings revealed nothing which seemed to cause death.

In order to make clear the real state and condition before and at the time of death, interviews were made to the remaining members of the family and to others concerned. The data obtained from the interviews were compared with the autopsy findings.

During the Second World War, there were some reports concerning the curious and sudden cardiac death in apparently healthy soldiers in Japan. In 1948, the Medical Examiner System was established to investigate this situation and it was revealed that there were many cases of curious cardiac death without pathological changes in autopsy.1,2 Such deaths occurred almost exclusively in the younger male individuals who seemed to be apparently healthy and lived their lives as usual until the day of death.

In general, they died suddenly during sleep with a groan as if having a dreadful dream. An agonizing deep respiration with stretching of the limbs were often noticed at the time of death. In such a case autopsy revealed nothing but ordinary manifestation caused by a sudden death. Moreover, chemical examination proved to be negative for all sorts of toxic agents, and no other apparent causes of death were found.

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Trifle changes revealed by autopsy had no particular relationship to the cause of death. These changes were as follows:

1) Marked congestion in all organs.
2) Congestion in all mucosa and serosa.
3) Blood of dark reddish purple colour with non-coagulating nature.
4) The amount of blood in the left heart was especially larger than that in the right heart.
5) Edema of the lungs, liver, kidney and pharyngolarynx.
6) The diffuse vacuolar formation and numerous vacuoles in the myocardial fibers were observed in some cases. And some of them were edematously swollen.
7) As regard to the distribution of the coronary artery, Group I according to Schleisinger's classification (The type in which the right coronary artery predominates the left) was observed in a high percentage in these cases in comparison with the control group. In some cases, an anomalous distribution of the coronary artery or under-developed heart and aorta were observed.

Over 100 cases of such curious and sudden death were seen annually in Tokyo and have gradually drawn the attention of many investigators. In the Tokyo Medical Examiner Office, this type of sudden death has been called as "Pokkuri disease." (Pokkuri means a sudden and unexpected occurrence in colloquial Japanese language.) Many investigators have exerted their utmost efforts to clarify the origin of these deaths. However, there have been only little clinical reports concerning this subject in the past.

Therefore, we have made some investigations on this problem in order to find the actual situation and causative mechanism of this probable acute cardiac death of unknown etiology.

**Material and Method**

A total 283 cases were selected as "acute cardiac death of unknown etiology" by autopsy at the Tokyo Medical Examiner Office from January 1959 to April 1961.

1. Through repeated interviews (from one to several times) with the family of the deceased and others concerned (namely, their friends and relatives, neighbourhood people, co-workers, doctors and so on), the occupation, past history, housing environment, diet, tabacco and alcohol consumption etc., emotional and physical state, drugs commonly used, and the circumstance of their death were studied. The data on 185 cases out of 283 cases were suitable for the investigation. These data were investigated along with their autopsy findings.

The autopsy findings and the classifications were as follows:

1) $A_1$: The hypoplastic group of coronary artery, heart and aorta.
A2: The group in which the slight degenerative changes in the myocardium were observed microscopically.
A3: Normal group in coronary artery, heart and aorta.
A4: The group with slight coronary sclerosis.

2) Cases were divided into 2 groups based on presence or absence of moderate pleural adhesion.
3) Cases were divided into 2 groups based on presence or absence of parenchyma of thymus.

These groups in 1) to 3) were investigated in comparison with the results of the interviews in detail.
4) The ratio of heart weight to body weight.
5) The ratio of adrenal weight to body weight.
6) The ratio of thyroid weight to body weight.
7) The ratio of thymus weight to body weight.
8) The thickness of the adrenal cortex.

The items in 4) to 8) were also investigated in comparison with the results of the interviews in detail.

II. From the interviews, it was found that there were 2 family trees in which 2 cases of the brothers died of acute cardiac death of unknown etiology. Each one of the brothers of the deceased cases was hospitalized and examined clinically.

RESULTS

No differences were observed as to the area distribution of these cases in Tokyo. However, such investigation has not been carried out on other areas, therefore we are not certain whether there is any difference of its occurrence between Tokyo and other regions, particularly in the rural area.

The age at the incidence ranged from 13 to 48 years. About 58 per cent of 184 cases were from 20 to 29 yrs. The age distribution is shown in Fig. 1. The A1, the hypoplastic group as previously stated, ranged in the younger age group than the others.

![Fig. 1. Age distributions of acute cardiac death of unknown etiology autopsied from January 1959 to April 1961 in Tokyo.](image-url)
The sex incidence dominated mostly in male and the ratio of male to female was about 14:1. When the state of death in the male was compared with the female, 130 cases (84%) out of 155 cases died during sleep at night. In the female, only 1 case (8.3%) out of 13 cases died during sleep and the others died during awake. The man who had slight complaints of any type of illness which required medical aid was seen in only 13 cases out of 147. In comparison with the male, the female who had slight complaints of various illness was seen in 10 cases out of 15. The percentage was higher in the female than in male.

As to their occupation, the subjects were divided into several groups by the use of the classification for the census in Japan. The worker of skill was observed in 33 percent of 185 cases. The man in trades handling money (including workers in banks etc.) was 20.5 per cent, while the heavy laborer was less than expected and was observed in only 2.8 per cent.

As to the monthly incidence, in May, June and July, the occurrence of such death were most frequent and included 82 cases (36.7%) of 223 cases in all. On the other hand, in December, January and February, the occurrence was only 42 cases (17.9%). When these subjects were divided into 2 groups according to whether they died during sleep or while awake, the group which died during sleep were greater in number in May, June and July than in any other month as shown in Fig. 2.

As to the time of death, 125 cases died during 12 p.m. to 6 a.m.; 39 cases from 6 a.m. to 12 a.m.; 4 cases from 12 a.m. to 6 p.m.; and 13 cases from 6 p.m. to 12 p.m. in a total of 181 cases (Fig. 3). But, even
in the subjects who died while awake, the occurrence was greater at night than during the day-time.

Moderate adhesion of pleura was observed in 37 out of 185 cases. Except for 1 case, the time of death in the group having pleural adhesion occurred at night as shown in Fig. 4. Except for 2 cases, all died during sleep (Table I.). This was seen in a higher percentage comparing to the subject without pleural adhesion.
Table I. Correlation between the Sleep and Pleural Adhesion in the Acute Cardiac Death of Unknown Etiology

<table>
<thead>
<tr>
<th></th>
<th>During sleep</th>
<th>During awaking</th>
</tr>
</thead>
<tbody>
<tr>
<td>With pleural adhesion</td>
<td>31 cases</td>
<td>2 cases</td>
</tr>
<tr>
<td>Without pleural adhesion</td>
<td>107 cases</td>
<td>35 cases</td>
</tr>
</tbody>
</table>

The objective symptoms observed by those present at the time of death were as follows. Groan was heard in 74 cases (67%) out of 111 cases. According to the frequency, groan, cramp, abnormal respiration, syncope and cyanosis were observed as shown in Table II. Only 8 cases complained of their symptoms just prior to their death. Out of 8 cases, 5 complained of chest pain, 1 abdominal pain, 1 headache, 1 dyspnea.

Thirty cases had experienced attacks such as chest pain and syncope, the complaint of groaning, respiratory abnormality and cyanosis previously, but clinical examination at that time revealed no abnormality.

The factors which seemed to have relationship were studied.

a) As regard to alcoholic beverage, about 100 out of 172 drank occasionally, 29 of 172 drank habitually. On the other hand, 43 of 172 had never touched alcohol before their death. Heavy drinkers were seen in only 8 cases.

b) Sixty-six cases of 185 complained of easy fatigability before death.

c) Among 185 cases, 11 were students. In the student group, 6 cases died during the examination, 3 during sports, 1 during drinking and 1 was uncertain.

Table II. Objective Findings Immediately Prior to Acute Cardiac Death of Unknown Etiology

<table>
<thead>
<tr>
<th>Objective findings</th>
<th>No. of cases</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groan</td>
<td>74</td>
<td>67</td>
</tr>
<tr>
<td>Cramp</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Abnormal respiration</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Faint</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Agony</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Redness of face</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Foaming</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
d) Drugs commonly used: None in 92 out of 151 cases. Of the remaining, 27 used vitamins commonly.

As previously stated, hereditary disposition has been reported in idiopathic cardiomegaly in Europe and America. In some cases of acute cardiac death of unknown etiology, hereditary disposition was also suspected by Sugai.4),5)

As shown in Fig. 5, in the hypoplastic group of coronary artery, heart and/or aorta, familial incidence of cardiac death or cardiac disease

![Fig. 5](image)

Fig. 5. The occurrence (♀) of heart disease and/or acute cardiac death in the family of patients of acute cardiac death of unknown etiology. The pathological findings of thoracic aorta and/or coronary artery are divided into 3 groups.

![Fig. 6](image)

Fig. 6. The history of 2 families in which more than 2 men died of acute cardiac disease of unknown etiology.
was observed more frequently than in other groups.

In 2 families, as shown in Fig. 6, in which more than 2 cases of acute cardiac death of unknown etiology occurred, 2 of the remaining family members were hospitalized and various examination upon cardiovascular, endocrinological and autonomic nervous system were carried out. The results are as shown in Table III.

Table III. The Findings of Examination of 2 cases.
(In their families, more than 2 cases of acute cardiac death of unknown etiology were observed.)

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history</td>
<td>Typhoid fever</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Allergic rhinitis</td>
<td>Emphysema</td>
</tr>
<tr>
<td>Chief complaint</td>
<td>(−)</td>
<td>1. Occasional chest pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Headache</td>
</tr>
<tr>
<td>Focal infection</td>
<td>Chronic pharyngitis</td>
<td>(−)</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td></td>
<td>(++)</td>
<td>(++)</td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td>Aschner's and Czermak's test</td>
<td>(+)</td>
</tr>
<tr>
<td></td>
<td>Epinephrine test</td>
<td>(++)</td>
</tr>
<tr>
<td></td>
<td>Pilocarpine test</td>
<td>(+)</td>
</tr>
<tr>
<td></td>
<td>Atropine test</td>
<td>(±)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±)</td>
</tr>
<tr>
<td>Thorn's test</td>
<td>-35%</td>
<td>-64%</td>
</tr>
<tr>
<td>Endocrine system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 K.S.</td>
<td>1.75 mg./day</td>
<td>4.39 mg./day</td>
</tr>
<tr>
<td>17 O.H.C.S.</td>
<td>3.10 mg./day</td>
<td>5.21 mg./day</td>
</tr>
<tr>
<td>Gonadotropin</td>
<td>3 units/day</td>
<td>6 units/day</td>
</tr>
<tr>
<td>Catecholamine</td>
<td>Normal range but variable tendency</td>
<td>Normal range but variable tendency</td>
</tr>
<tr>
<td>5 H.I.A.A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sayada's reaction of urine</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>After parenteral administration of vitamin B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>After oral administration of Belladonna extract</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>Basal metabolic rate</td>
<td>-12.5%</td>
<td>-7.5%</td>
</tr>
<tr>
<td>Artery of fundus oculi</td>
<td></td>
<td>Slight narrowing</td>
</tr>
<tr>
<td>Character</td>
<td>Introvert</td>
<td>Neurotic tendency, introvert</td>
</tr>
</tbody>
</table>
Pathological Investigation
a) Adrenal glands
As shown in Fig. 7, the ratio of adrenal weight to body weight was smaller than the control group as described by Aimi et al. The microscopic examination on the adrenals in these cases revealed the thinning of adrenal cortex, in which the fascicular zone was thinner, and in which the glomerular zone was thicker than that of the control group (Fig. 8). The scantiness of lipoid in these adrenals was also seen (Fig. 9).
However, there were no relationships between the grade of the pathological features in the adrenals and the results of the interviews.

b) Autonomic ganglion

The superior and inferior cervical ganglion displayed a considerable degree of atrophy and degeneration, namely the appearance of "ragged cell" (Fig. 10), an increased hyperplastic accessory cell (Fig. 10) or the formation of the vacuoles in the ganglion cell (Fig. 11). Also the parasympathetic ganglion cells were seen in the cervical ganglion (Fig. 11).
c) Thymus

The average weight of the thymus in these cases were remarkably greater than that of the control group. Microscopically, the thymus was parenchymatous and contained abundant cortical lymphoid cells in many cases. While in the group in which the parenchymatous thymus was recognized, 88 out of 110 (80%) died during sleep; in the group in which no parenchymatous thymus was seen, 29 of 52 (55%) died during sleep.

**COMMENT**

The origin and the causative factors of "acute cardiac death of unknown etiology" are still unknown, though many factors are under consideration. It is interesting to note that there are little reports of such death as we have described here except in Japan. However, "Bangungut" reported by Cruz or "Curious death in soldier" reported by Moritz and Zamcheck, seem to be similar to the subject of our study.

The reports on "acute cardiac death of unknown etiology" in Europe and America were all stated with respect to "idiopathic cardiac hypertrophy", therefore it is different from our cases.

Could these deaths be lesser in Europe and America than in Japan? Or could the same death as our cases been called by other names, such as coronary heart disease due to the difference of opinion between Japan and Europe and/or America? Further investigation must be made on these points.

As Sugai pointed out previously, in our sudden cardiac death some cases were suspected to have status thymicolymphaticus. Also, in many cases, there were hypoplastic cases of coronary artery, heart and aorta. The existence of congenital disposition was suggested in some cases by
Our investigation also revealed some families in which many cardiac deaths occurred, especially in the group of hypoplastic coronary artery, heart and/or aorta. Though these facts are indeed one of the important factors of "acute cardiac death of unknown etiology," these were not always seen in all cases and did not seem to be the final or the essential factor.

From the following facts such as, complaints of feeling of fatigue and decreased sexual desire in the married man just before the death, the student's death during examination or sports, and the hypofunction of adrenals, the degeneration of autonomic ganglion suggests the presence of "Exhaustion Stage" described by Selye.

It is interesting that these deaths occurred mostly in May, June and July, while the deaths due to organic heart disease occurred mostly in the winter months.

The fact that the subjects died during sleep at night, especially in those having pleural adhesion, in a high percentage seemed to correlate with the vagal reflex, as Leschke's statement "Die Nacht ist der Zeit des Vagus". Jude also suggests that the greatest of cardiac arrest is due to vago-vagal reflex. Moreover, there could possibly be some cases with Adams-Stokes attack and some cases with hypotensive attack as adrenal collapse at the time of death.

From our data, the differences of the state at the time of death was observed between the male and the female, and between the group dying during sleep and awake. Also, there are various types of complaints in "acute cardiac death of unknown etiology." These facts indicate that the mechanism of the death is not always identical and that there are various types.

From our present study, the mechanism and etiology of such acute cardiac death of unknown etiology were uncertain though some neurohumoral factors such as the hypofunction of adrenals, dysfunction of the autonomic nervous system and so on might be concerned. Further investigation is necessary.

Summary

(1) Investigation was made on 283 cases which were decided as "acute cardiac death of unknown etiology" (the so called "Pokkuri disease" in Japanese) by autopsy at the Tokyo Medical Examiner Office.

(2) Apparently healthy young males were most common among the groups and they died abruptly during sleep at night. The cause of death was not found by autopsy or biochemical examination.

(3) Our subjects were different from the "acute cardiac sudden
death of unknown etiology” reported in Europe and America. Deaths similar to that found in our country are not reported in such countries.

(4) From our study, the neurohumoral system, especially the adrenal gland and the autonomic nervous system appear to play an important role in the causative mechanism of “acute cardiac death of unknown etiology.”

ACKNOWLEDGMENT

The authors wish to express their thanks to Misses R. Yuasa, M. Kuroda, M. Aoki, M. Toriyama, E. Sugimoto, T. Sasaki, M. Amasawa, M. Morimoto, A. Obara, H. Ohtsuka (Department of Health Care and Nursing, Faculty of Medicine, University of Toyko), Miss A. Hirayama (Institute of Public Health) and Miss M. Motegi (Mitsui Kosei Hospital) for their co-operation throughout this investigation.

REFERENCES