CHARACTERISATION OF CLASSICAL SUDDEN INFANT DEATH SYNDROME (SIDS) AND GRAY ZONE SIDS IN JAPAN USING JAPANESE PATHOLOGY AND AUTOPSY REPORT (1982-1986) FROM THE JAPANESE SOCIETY OF PATHOLOGY

Japon Patoloji Cemiyetinden Klasik Ani Beşik Ölümü Sendromu Özellikleri (SIDS) ile Japon Patoloji ve Otopsi Raporlarına Bağlı Japonlardaki Tartışmalı Ani Beşik Ölümleri (1982-1986)

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Sawaguchia T, Fujitab T, Kobayashic M, Sawaguchia A. Characterisation of Classical Sudden infant Death Syndrome (SIDS) and Gray Zone SiDS in Japan using Japanese Pathology and Autopsy Report (1982-1986) from The Japanese Society of Pathology, Adli Tıp Bülteni; 1996; 1(2): 58-63.

ABSTRACT

There is no standardised criterion on the handling of Classical Sudden Infant Death Syndrome (SIDS) and Gray Zone SIDS. Particularly international discussion is needed on the handling of Gray Zone cases. Autopsy findings for Classical SIDS and Gray Zone SIDS in Japan has been analysed in preparing the basic data for this discussion in this report.

The material analysed was found in the Japanese Pathology and Autopsy Report from the Japanese Society of Pathology (January 1982 to December 1986). A x^2 test was required to find the difference between Classical SIDS and Gray Zone SIDS in each autopsy finding. In addition, factor analysis (the principal factor method with Varimax rotation) was carried out to identify the structure of the autopsy findings not only for Gray Zone SIDS but also for Classical SIDS.

Using the x^2 test a lymph tissue enlargement was found to have a high statistical value in Classical SIDS. Congestion, thymus enlargement, pulmonary oedema, adrenal gland atrophy, lymph tissue enlargement and neonate were recorded with high factor loadings in Classical SIDS by factor analysis.

Pneumonia, premature baby, and cardiomegaly was recorded with high statistical value in Gray Zone SIDS by the x^2 test. Asphyxia, congestion, atelectasis, pulmonary emphysema, adrenal gland atrophy, premature baby, thymus hypoplasia, cardial malformation and ectopic hemopoesis were recorded as having high factor loadings in Gray Zone SIDS using factor analysis. Thymus enlargement and adrenal gland atrophy were recorded in the third factor of Gray Zone SIDS having rather high negative factor loading using factor analysis.

It is remarkable that asphyxia was extracted in the first factor of Gray Zone SIDS with the highest loading factor using factor analysis. This fact might suggest indirectly that a percentage of Gray Zone SIDS would be underdiagnosed because of a substitutional diagnosis of asphyxia as being an external cause of death in Japan, even in general pathological autopsies during 1982 to 1986.

Key Words: Sudden Infant Death Syndrome (SIDS), Classical SIDS, Gray Zone SIDS, Japanese Pathology and Autopsy Report, Factor Analysis

ÖZET

Klasik Ani Beşik Ölümü Sendromlarının ve Tartışmalı Ani Beşik Ölümü Sendromlarının incelenmesinde standart kriterler bulunmamaktadır. Özellikle Tartışmalı Ani Beşik Ölümü Sendromlarının değerlendirilmesinde uluslararası tartışma gerekmektedir. Japonya'daki Klasik Ani Beşik Ölümü Sendromlarının ve Tartışmalı Ani Beşik Ölümü Sendromlarının otopsi bulguları değerlendirilerek tartışma için temel veriler bu raporda sunulmuştur.

Japon Patoloji Cemiyeti'nden alınan Japon Patoloji ve Otopsi Rapor'u (Ocak 1982) Aralık 1986) incelenmiştir. Klasik Ani Beşik Ölümü Sendromlarının ve Tartışmalı Ani Beşik ölümü Sendromlarının otopsi bulgularının farklarının bulunmasında ki-kare testinin kullanılması gerekmiştir. Ek olarak sadece Tartışmalı Ani Beşik Ölümü Sendromlarının otopsi bulgularının değil aynı zamanda Klasik Ani Beşik

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Ölümü Sendromlarının otopsi bulgularının yapısını da göstermek amacıyla faktör analizi (Varimax rotasyonu ile beraber temal faktör metodu) yapılmıştır.

Ki-kare testi incelenmesinde lenf dokusu büyümesinin Klasik Ani Beşik Ölümü Sendromlarında oldukça anlamlı olduğu bulunmuştur. Konjesyon, timus büyümesi, pulmoner ödem, adrenal bezi atofisi, lenf dokusu büyümesi ve yenidoğan olma bulguları Klasik Ani Beşik Ölümü sendromunda faktör analizi yöntemi ile yüksek değer taşıdığı bulunmuştur.

Ki-kare testi ile pnömoni, prematür bebek ve kardiomegali bulguları Tartışmalı Ani Beşik Ölümü Sendromu için oldukça anlamlı bulunmuştur. Asfiksi, konjesyon, atelektazi, pulmoner amfizem, adrenal bez atrofisi, prematür bebek, timus hipoplazisi, kalp malformasyonu ve ektopik hemopoesis bulgularının Tartışmalı Ani Beşik Ölümü sendromunda faktör analizi yöntemi ile yüksek değer taşıdığı bulunmuştur.Timus büyümesi ve adrenal bez atrofisinin Tartışmalı Ani Beşik Ölümü Sendromlarında oldukça yüksek negatif değer taşıdığı bulunmuştur.

Tartışmalı Ani Beşik Ölümü Sendromlarında faktör analizi yöntemi ile en yüksek değer ile birinci faktörde asfiksinin hariç tutulduğu dikkat çekicidir. Bu bulgu Tartışmalı Ani Beşik Ölümü Sendromlarının bir bölümünün 1982-1986 yılları arasında genel patolojik otopsilerde bile harici bir ölüm sebebi olarak kabul edilen asfiksi tanısı konularak kayıtlara girmediğini dolaylı olarak gösteriyor olabilir.

Anahtar kelimeler: Ani beşik Ölümü Sendromu (SIDS), Klasik SIDS, Tartışmalı SIDS, Japon Patoloji ve Otopsi Raporu, Faktör Analizi.

INTRODUCTION

At the Second National Institute of Child Health and Human Development (NICHHD) Conference held at Seattle in 1969, it was stated that an autopsy is mandatory for the diagnosis of SIDS (1). However, the definition by the Ministry of Health and Welfare of the Japanese Government had dual standards (broad and narrow definitions) (2). In 1995, this dual definition was changed and the broad definition was abolished (3). As a result of this change, an autopsy is now required for the diagnosis of SIDS in Japan.

For an accurate diagnosis of SIDS, the precision of the autopsy is important. Actually the diagnosis of SIDS is sometimes difficult even after autopsy. One of the reasons for this is determining whether Gray Zone SIDS or Classical SIDS (4) is in evidence. A diagnostic decision for Gray Zone SIDS depends on the countries making the examination and is not formally determined by an international standard.

As to the recent diagnostic accuracy of SIDS that were determined under general pathological autopsy in Japan, there was no tendency for extreme overdiagnosis and underdiagnosis in the previous study using Japanese Pathology and Autopsy Report (January 1987 to December 1991) (5,6) including only general pathological autopsies, after detailed analysis, it was obvious that there were some Gray Zone SIDS cases diagnosed as just "sudden death". In these cases, most of the clinical diagnosis were SIDS and most of the pathological diagnosis were just "sudden death". These decision depended on a few specific medical centres.

In addition, to the recent diagnostic tendency of SIDS that was made under all autopsies including forensic autopsy and general pathological autopsies, asphyxia and misaspiration were extracted as Gray Zone SIDS cases as the first and second factor with high factor loading by factor analysis in the previous study using the following Survey Sheets for Death: Vital Statistics from the Japanese Ministry of Health and Welfare (7) (January 1990-to December 1992). This fact might suggest indirectly that a percentage of Gray Zone SIDS had been underdiagnosed by the substitutional diagnosis of asphyxia as an external cause of death in Japan under forensic autopsies even recently.

The purpose of this report is to analyse the diagnostic tendency of SIDS using general pathologic autopsies in Japan from 1982- 1986 and to provide a comparative analysis of the difference in autopsical findings between Gray Zone SIDS and Classical SIDS in Japan. It might be useful to compare the results of this study with our previous research (6,7) and thereby grasp the change in diagnostic tendency of Gray Zone SIDS in Japan.

The result of this study might be useful, for discussion, as basic data to clarify Classical SIDS and Gray Zone SIDS and prepare an international standardised criterion.

MATERIAL AND METHODS

The materials analysed were from Japanese Pathology and Autopsy Report from the Japanese Society of Pathology (January 1982 to December 1986). In this report, all of the organisations where it is possible to carry out general pathological autopsies including medical universities, medical colleges, national & general hospitals and medical centres in Japan are entered and the records of all pathological autopsy cases of these organisations are summarised. From these summarised autopsy protocols, sudden death cases of infants under two years old were selected for this study.

Discrimination between Gray Zone SIDS and Classical SIDS was carried out by the SIDS project committee in Tokyo Women's Medical College using Beckwith's (1) and Willinger's reference (4) and the following categories (8) :

1. Pure SIDS cases, in which the autopsy and clinical information do not reveal any cause of death.

2. Borderline SIDS cases, in which pre-existing congenital disorders or clinical symptoms, and/or post-mortem findings, are not severe enough to explain the cause of death.
3. Non-SIDs cases, in which the cause of death is explained according to clinical information and/or the results of the post-mortem examination.

Two forms of analysis were used. One was the analysis of the difference of the incidence of each autopsy finding for which the x^2 analysis was used.

The other was the factor analysis of structural relationship of the total autopsy findings (6). These analyses were carried out independently on two groups (Classical SIDS and Gray Zone SIDS).

For the factor analysis, 167 autopsy findings found recorded were contracted to 114 due to unification. Then autopsy findings which are positive in more than four positive cases were sampled for Classical SIDS and more than three positive cases were sampled for gray Zone SIDS. As a result, 17 autopsy findings in Classical SIDS and 26 autopsy findings in gray Zone SIDS were selected. This factor analysis depended on the principle factor method with Varimax rotation, sampling three factors with higher rank according to the proportion of variance.

RESULT

1) The Characteristics of Autopsy Findings

The frequencies and the x^2 analysis of autopsy findings in each of the two groups are shown in Table

Table 1. Frequency of Autopsy Findings in SIDS (Classical SIDS & Grayzone SIDS)

Autopsy Findings	Classical SIDS		Grayzone SIDS		P value
	n	%	n	%	
gliosis	1	1.9	1	2.4	1
enlargement of lymph node	16**	30.2	4	9.8	0.032
mucous membrane degeneration	3	5.7	1	2.4	0.801
discephalia of mandibulae	0	0	1	2.4	0.897
splenitis	0	0	2	4.9	0.366
fatty liver	4	7.5	8	19.5	0.158
liver enlargement	2	3.8	3	7.3	0.767
bronchitis	8	15.1	7	17.1	1
enteritis	2	3.8	1	2.4	1
ischaemic changes	2	3.8	0	0	0.592
thymus enlargement	14*	26.4	4	9.8	0.077
displasia of lung lobe	1	1.9	1	2.4	1
congestion	26	49.1	15	36.6	0.318
external malformation	2	3.8	2	4.9	1
petechiae	3	5.7	0	0	0.339
brain oedema	7	13.2	6	14.6	1
pneumonia	4	7.5	22***	53.7	0
disexpansion of lung	2	3.8	1	2.4	0.235
pulmonary microembolism	1	1.9	0	0	1
pulmonary oedema	12	22.6	6	14.6	1
bleeding in adrenal glands	0	0	2	4.9	0.475
chronic infection	2	3.8	0	0	0.366
ovarian cyst	3	5.7	0	0	0.592
exogenous hemopoiesis	3	5.7	4	9.8	0.338
cardiovascular malformation	3	5.7	6	14.6	0.723
misaspiration	1	1.9	3	7.3	0.266
organ dysgenesis	0	0	1	2.4	0.436
brain degeneration	0	0	1	4.5	0.897
asphyxia	0	0	1	7.3	0.159
adrenal gland hypoplasia	4	7.5	0	0	0.2
thymus hypoplasia	0	0	4*	9.8	0.071
subarachnoid haemorrhage	0	0	3	7.3	0.159
cardiomegaly	0	0	5**	12.2	0.032
myocarditis	0	0	3	7.3	0.159
immaturity of baby	0	0	6**	14.6	0.014

*p<0.10
**p<0.05
***p<0.01

Table 2. Characteristic Autopsy Findings of Classical SIDS and Grayzone SIDS

	Autopsy Findings
Classical SIDS	Lymph tissue enlargement**
	Thymus enlargement*
Grayzone SIDS	Pneumonia***
	Thymus hypoplasia*
	Cardiomegaly**
	Immaturity of baby**

* $p<0.10$
** $p<0.05$
*** $p<0.01$

Table 3. Structure of Autopsy Findings of Classical SIDS in Japanese Pathology and Autopsy Report (factor Loading Matrix)

Variables	Factor Loading
First Factor (proportion of variance 19.7 %)	
liver congestion	0.909
spleen congestion	0.908
kidney congestion	0.903
pulmonary congestion	0.59
neonate	0.495
Second Factor (proportion of variance 12.5%)	
adrenal glands atrophy	0.691
pulmonary oedema	0.575
lymph tissue enlargement	0.559
thymus enlargement	0.542
congestion of total body	0.517
Third Factor (proportion of variance 11.5 %)	
adrenal glands hypoplasia	0.643
thymus enlargement	0.508

1. The autopsy findings with more than a 10 % significant level are shown in Table 2.

From these two tables, it was recognised that Classical SIDS in Japan was characterised by thymus enlargement and lymph tissue enlargement. It was also found that in Gray Zone SIDS pneumonia, premature baby, cardiomegaly and thymus hypoplasia were of a significant value.

2) The Structure of Autopsy Findings

The result of factor analysis is shown in Table 4. In the factor analysis, the proportion of variance by the three factors sampled was 44.2 % in Classical SIDS and 35.2 % in Gray Zone SIDS. Each of the autopsy findings including a factor loading of more than o.495 are shown in Table 3 and Table 4.

In the first factor of Classical SIDS, congestion in liver, spleen, kidney and lung showed positive high factor loadings. And neonate showed the next positive high factor loading. This suggests the first factor reflects the congestion of organs and neonate also shows congestion in many case. In the second and third factors of Classical SIDS adrenal glands atrophy and/or hypoplasia, lymphoid tissue enlargement, thymus enlargement showed positive high factor loadings. This seems to suggest that these two factors reflect so called status thymicus. In addition, the second factor is associated with the total hypervolemic state reflecting pulmonary oedema and congestion of total body.

Table 4. Structure of Autopsy Findings of Grayzone SIDS in Japanese Pathology and Autopsy Report (Factor Loading Matrix)

Variables	Factor Loading
First Factor (proportion of variance 14.1 %)	
asphyyxia	0.797
kidney congestion	0.756
spleen congestion	0.727
liver congestion	0.694
atelectesis	0.51
pulmonary emphysema	0.53
Second factor (proportion of variance 11.5 %)	
fatty changes of liver	-0.762
brain oedema	-0.732
Third Factor (proportion of varience 9.4 %)	
premature baby	0.568
thymus hypoplasia	0.547
congenital heart anomaly	0.542
exogenous hemopoiesis	0.505
thymus enlargement	-0.495
adrenal glands atrophy	-0.495

In the first factor of Gray Zone SIDS, asphyxia showed the highest positive factor loading and the congestion of organs as the signs of asphyxia also showed the next highest positive factor loadings. In addition, pulmonary emphysema and atelectasis showed the next highest positive loadings. This suggests that asphyxia, pulmonary emphysema and atelectasis might be general factors which confuse the diagnosis of SIDS. In the second factor of Gray Zone SIDS, fatty changes in liver and brain oedema showed high negative factor loadings. This suggest these findings might be easy to be clarified as part of the Classical SIDs group. In the third factor of Gray Zone SIDS, premature baby, congenital heart anomaly and exogenous hemopoesis showed high positive factor loadings. Thymus hypoplasia showed a positive factor loading and simultaneously thymus enlargement and adrenal glands atrophy showed high negative factor loadings. This fact contrasts with the results found for the second and third factors of Classical SIDS.

DISCUSSION

From above results, some characteristic points are suggested.

At first, in Classical SIDS, the hypervolemic state including congestion and pulmonary oedema was the

main factor. It was remarkable that neonate showed a rather high factor loading in the first factor of Classical SIDS. Sudden death in early neonatal stage is not included in the SIDS definition in most European countries and the U.S.A., only the cases which lived for more than 28 days had previously been counted as SIDS, but recently cases which have lived for more than 7 days have been counted statistically (7). On the other hand in Japan, SIDS is recognised prior to 7 days after birth. In the previous survey by Yamanami et al (8), the incidence of SIDS and ALTE in early neonatal stage was 0.09 per 1000 of births in Japan and this value was equal to one fifth of the incidence of SIDS in Japan. Internationally the relationship between neonatal sudden death and SIDS has been under discussion.

Secondly, some findings suggesting status thymicus like thymus enlargement and adrenal glands atrophy or hypoplasia showed high factor loadings in the second and third factors in Classical SIDS. Fortunately in contrast, in the third factor in Gray Zone SIDS thymus hypoplasia showed a high positive factor loading and thymus enlargement and adrenal glands atrophy showed rather high negative factor loadings. These facts seem to suggest a correlation between status thymics and SIDS. On this point a further study, in which the correlation between the weight of thymus or adrenal glands and SIDS is statistically evaluated, should be carried out. Generally speaking, thymus enlargement in SIDS seems to be a false positive because the hormone from the adrenal glands has not been released at the time of sudden death, the thymus appears normal and the so called status thymics is now not used in this connotation academically. In spite of this view point, some pathologists have pointed out that there is thymus enlargement in many SIDS cases. In this study the association between thymus hypoplasia and Gray Zone SIDS was reported. This point had not been reported previously.

Thirdly, asphyxia showed the highest positive factor loading in the first factor in Gray Zone SIDS. A percentage of Gray Zone SIDS might be underdiagnosed because of the substitutional diagnosis of asphyxia as an external cause of death in Japan under general pathological autopsies during 1982-1986. In a previous study using Survey sheets for Deaths (1990-1991) (7), similar tendency was recognised. The diagnosis as asphyxia seems to be characteristic of the diagnosis of gray Zone SIDS in Japan.

Lastly, most of the findings which showed a high factor loading in Gray Zone SIDS like pulmonary emphysema, atelectasis, fatty change of liver, brain oedema, congenital heart anomaly and premature baby are the important factors which certify the difference between Classical SIDS and Gray Zone SIDS. As to these findings, a quantitative standard should be prepared as a criterion. The criteria in a previous Nordic study (8) was partially standardised quantitatively. Particularly the infection as a finding of lung was shown quantitatively. Therefore this criteria was very useful.

There is no standardised criterion for the handling of Classical SIDS and Gray Zone SIDS. The author thinks that a detailed criterion with definite quantitative standards should be prepared under international discussion.

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REFERENCES:

1. Bechwith JB. Discussion of Terminology and Definition of the Sudden Infant Death Syndrome. In Bergmann AB, Bechwith JB, Ray CG (Eds) Proc Death in Infants. Washington Press, Seatle, 1969:14-22.

2.Togari H, Kato I. The Study of the Definition of Sudden Infant Death Syndrome (SIDS). In Kato Y (eds) Research Report of the Study for the Prevention and Treatment System of Physical and Mental States of Children. Ministry of Health and Welfare, Tokyo, 1994:238-241.

3. Togari H, Kato I. The Study of the Definition of Sudden Infant Death Syndrome (SIDS). In Kato Y (eds) Research Report of the Study for the Prevention and Treatment System of Physical and Mental States of Children. Ministry of Health and Welfare, Tokyo, 1994:221-225.

4. Willinger M, James S, Catz C. Defining the Sudden Infant Death Syndrome (SIDS). Pediatr. Pathol.1991;11:677-684.

5. Sawaguchi T, Sawaguchi A, Fujita T, Kobayashi M. Statistical Estimation of Frequency and Diagnostic Accuracy of Sudden Infant Death Syndrome in Japan. Res.Pract. Forens.Med. 1994;37:397-401.

6. Sawaguchi T, Sawaguchi A, Fujita T, Kobayashi M. Statistical Estimation of Diagnostic Accuracy of Sudden Infant Death Syndrome in Japan. Rom J Leg. Med. 1994;2:123-129.

7 . Sawaguchi T, Fujita T, Sawaguchi A. Characterisation of Gray Zone Sudden Infant death Syndrome (SIDS) in Japan using Survey Sheets for Death: Vital Statistics from the Ministry of Health and Welfare (1995) Rom.J.Leg.Med. in print.

8. Gregersen M, Rajs J, Laursen H, Baandrup U, Frederriksen P, Gidlund E, Helweg-Larsen K, Hirvonen J, Isaksen CV, Kock K, Lundemose JB, Loberg EM, Rognum TO, Skullerund K, Vege A. Pathologic Criteria for the Nordic Study of SIDS. In Rognum TO (eds) Sudden Infant Death Syndrome. New Trends in the Nineties. Scandinavian University Press, Oslo, 1995:50-58.

9. Shiba S. The method of Factor Analysis. Tokyo University press Tokyo 1986:16-46 & 105-126.

10. Kato I, Togari H. Epidemiological Study of Neonatal Sudden Death. Perinatal Medicine. 1992;22:333-336.

10. Yamanami S, Nishioka M, Tanaka H, Oku K. The Whole Country Investigation of SIDS and ALTE in Early Neonatal Stage. Research Report of the Study for the Prevention and Treatment System of Physical and Mental States of Children. Ministry of Health and Welfare, Tokyo, 1995:245-250.