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Sudden Infant Death Syndrome: Measurement of Total and Specific Serum Immunoglobulin E (IgE)

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ABSTRACT: Postmortem evaluation of total and specific serum immunoglobulin E (IgE) antibody levels by the paper radio immuno sorbent test (PRIST) and radio allergo sorbent test (RAST), respectively, revealed that there was no significant elevations in total circulating IgE or in specific IgE antibodies to house dust, *Dermatophagoides farinae* (house dust mite), *Alterarnia tenuis* (mold), or milk proteins for sudden infant death syndrome (SIDS) victims when compared to a control group.

KEYWORDS: pathology and biology, sudden infant death syndrome, immunoglobulins

That an allergic reaction to cow's milk or other common allergen might be a causative factor in sudden infant death syndrome (SIDS) has long been considered plausible and is presently receiving reserved scrutiny as a result in part of advances in the in vitro diagnosis of allergy.

In the early 1960s Parish et al [*1,2*] performed a series of elegant and intriguing experiments showing that lightly anesthetized guinea pigs, which had previously been sensitized to milk proteins would, on the introduction of a small amount of milk protein into the lungs, die in a manner that clinically and pathologically resembled that seen in SIDS. Devey et al [*3*] showed that the fatal sensitization to cow's milk could come from ingestion alone. At the same time, Gunther et al [*4*] using the tanned red cell technique of Boyden [*5*], showed that most normal infants fed on cow's milk developed antibodies to the protein, and Hunter et al [*6*], shortly thereafter, made detailed studies of the immunoglobulin classes of antibodies to cow's milk and theorized that some may belong to the (then) newly discovered immunoglobulin E (IgE) class.

In 1973 Clausen [*7*], using a radioimmunoassay for IgE, was unable to detect significantly higher levels in SIDS victims than controls. Turner et al [*8*] in Australia concurred, but did find elevated levels of specific antibodies to milk, mold, and dust mite in SIDS victims and suggested that hypersensitivity should seriously be considered as a possible factor in the etiology of SIDS.

Recently, Clark et al [*9*] were unable to reproduce Turner's findings and concluded that there was no evidence that these allergens were implicated in the pathogenesis of SIDS.

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The purpose of this study was to investigate the possible role of an IgE mediated hypersensitivity to common allergens in the deaths of SIDS victims in Wayne County, MI.

Materials and Methods

Serum samples were obtained over a three-year period (1977 to 1979) from cases presented to the Wayne County Medical Examiner's Office. The basis for determination of SIDS and autopsy protocols have been described at length elsewhere [*10*]. By definition, SIDS is the sudden death of any infant or young child which is unexpected by history and in which thorough postmortem examination fails to demonstrate an adequate cause of death [*11*]. Postmortem samples, obtained from infants dying of other causes, served as a control group. All of the samples were from infants less than one year of age. The sera were stored at −20°C until used.

Measurement of IgE Levels

Total IgE was measured using the paper radioimmuno sorbent test (PRIST) method (Pharmacia Laboratories, Piscataway, NJ). Briefly, sera were incubated 3 h at room temperature with sheep anti-IgE bound to paper discs. After washing, the discs were incubated 18 h at room temperature with rabbit anti-IgE ^{125}I. After a second wash, the radioactivity bound to the discs was quantitated in a gamma counter and total IgE determined by reference to a standard curve using human IgE in a serum matrix. The procedure is a sensitive one and has an effective range of 0.5 to 100 μL/mL with undiluted samples. A unit of IgE is approximately 2.43 ng.

Measurement of Specific IgE Antibodies

Specific IgE antibodies were measured using the radio allergo sorbent test (RAST), (Pharmacia Laboratories, Piscataway, NJ). The sera were incubated for 3 h at room temperature with specific allergens covalently bound to paper discs. After washing, the discs were incubated for 18 h at room temperature with rabbit anti-IgE ^{125}I. After a second wash, the radioactivity bound to the discs was quantitated in a gamma counter. Unknowns were compared to four reference sera covering the range of 0.35 to 17.5 Pharmacia Rast Units (PRU/mL). The allergens were selected based on their probable presence in the infant's local environment[4] and included: (1) milk proteins, (2) house dust (Holister-Stier), (3) *Alternaria tenuis* (a mold common to this geographic area), and (4) *Dermatophagoides farinae* (house dust mite). Holister-Stier house dust was chosen because it contains a wide range of allergens common to the home environment.

Results

Total and specific IgE levels were measured in 21 SIDS victims and 12 controls as indicated in Table 1. The total IgE is expressed in microlitres/millilitres with a unit equal to 2.43 ng. No significant difference was found between the SIDS and control sera. Two control cases had very high levels of total IgE (Cases 25 and 33). No significant increase in total IgE was found when compared to age-matched normal control ranges established by Kjellman et al [*12*]. Table 2 indicates the mean age, geometric mean total IgE, and range of values for the two groups. The data was not normally distributed as indicated by D'Agostino's test for normalcy [*13*], nor was it made so by e log conversion [*12*]. No significant difference between the two groups was determined by the Mann-Whitney nonparametric analogue to the *t* test [*13*].

[4]Personal communication, Holistier-Stier Laboratories, Spokane, WA.

TABLE 1—*Total and specific IgE in sera from SIDS victims and controls.*

Case Number	Age in Weeks	Cause of Death	Total IgE, μL/mL	Specific IgE			
				Milk	Dust Mite	Dust	Mold
1	4	SIDS	4.0	0	0	0	0
2	18	SIDS	17.0	0	0	0	0
3	16	SIDS	6.4	0	0	0	0
4	8	SIDS	5.4	0	0	0	0
5	8	SIDS	3.6	0	0	0	0
6	6	SIDS	3.8	0	0	0	0
7	6	SIDS	1.6	0	0	0	0
8	7	SIDS	1.7	0	0	0	0
9	22	SIDS	31.0	0	0	0	0
10	12	SIDS	6.7	0	0	0	0
11	4	SIDS	1.3	0	0	0	0
12	20	SIDS	3.1	0	0	0	0
13	16	SIDS	3.7	0	0	0	0
14	28	SIDS	9.0	0	0	0	0
15	12	SIDS	1.3	0	0	0	0
16	16	SIDS	3.7	0	0	0	0
17	12	SIDS	11.8	0	0	0	0
18	10	SIDS	3.1	0	0	0	0
19	12	SIDS	1.0	0	0	0	0
20	8	SIDS	3.5	0	0	0	0
21	14	SIDS	14.3	0	0	0	0
22	56	myocarditis	6.9	0	0	0	0
23	44	hydrocephalus	9.1	0	0	0	0
24	24	subendocardial fibrosis	2.9	0	0	0	0
25	3	dehydration, gastroenteritis	85.1	+1	QNS[a]	QNS	QNS
26	12	Reye's syndrome	0.6	0	0	0	0
27	12	encephalitis	2.8	0	0	0	0
28	60	asphyxia	10.3	+2	0	0	+2
29	20	multiple injuries	10.5	0	0	0	0
30	12	pneumonia	23.5	0	0	0	0
31	56	accidental hanging	2.6	0	0	0	0
32	16	bronchitis	3.6	0	0	0	0
33	40	multiple injuries	100.0	0	0	0	0

[a]QNS = quantity not sufficient.

TABLE 2—*Mean total IgE for SIDS and controls.*

	N	Mean Age in Weeks	Geometric Mean, μL/mL	Range
SIDS	21	12.3	4.3	1.0 to 31.0
Controls	12	29.6	7.9	0.6 to 100.0

The specific IgE antibody results are expressed as 0(<0.35 PRU/mL), +1 (0.35 − 0.7 PRU/mL), +2 (0.7 − 3.5 PRU/mL), +3 (3.5 − 17.5 PRU/mL), and +4 (≥17.5 PRU/mL). A result of +1 would correspond to approximately 1 to 5 μm/mL of specific IgE. Attempts to read levels between 0 and 0.35 PRU by extrapolation of the curve generated by the reference sera [*14*] did not provide values on any of the SIDS sera significantly greater than an IgE free (horse serum) standard. Two of the control sera showed elevated specific antibodies to milk proteins (Case 26 and 28) and *A. tenuis* (Case 28).

Discussion

The anaphylaxis theory of SIDS is an appealing one for several reasons. First, it would seem to explain some of the characteristic findings in SIDS [*15*]. The "cold-like" symptoms so often seen in the weeks before death might simply be indications of the victim's growing sensitivity to an allergen. The presence, on autopsy, of small quantities of regurgitated material in the lungs of SIDS victims and the almost universal feature of an apparent "silent" death during sleep after a meal appears to be comparable to Parish et al's [*1,2*] experimental findings with sensitized, lightly anesthetized guinea pigs.

Epidemiological studies relating age of SIDS victims and time of the year with environmental factors are interesting [*16,17*]. Hoppenbrouwers et al [*17*] demonstrated that peak levels of sulphur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and hydrocarbons (HC) during the winter months preceded the increase of SIDS by seven weeks. They felt that chronic exposure to envirnomental pollutants can lead to chronic hypoxia and decreased resistance to infection. The time of year and age distribution could also lend themselves to an anaphylactic explantation. An investigation of this theory is extremely important because of the ease of screening for hypersensitivity in the infants and the preventive measures that can be undertaken.

There are, however, problems with the anaphylaxis theory. As Turner [*8*] points out, in SIDS one does not find the systemic and localized eosinophilia that would be expected in a Type 1 hypersensitivity reaction. In none of our cases was eosinophilia found. There also has been a failure to show elevated levels of circulating antibodies of any class [*7*] in SIDS victims, and Raven [*18*] was unable to demonstrate any tissue bound IgE in the lungs of SIDS cases. Warnasuriya et al [*19*] failed to demonstrate any difference in frequency of atopic symptoms, response to immediate skin tests to various antigens (*D. pteronyssinus*, mixed grass pollen, cow's milk, egg, and shell fish), IgE, IgE antibody, immunoglobulin G, A, and M, or yeast opsonization in parents of SIDS victims from those of controls.

In this study we were unable to demonstrate any significant elevation of IgE, either total or specific, in SIDS victims. When interpreting this data, one should, however, consider the inherent difficulties in assessing IgE status.

1. It is difficult to establish "normal" levels of IgE in infants. At least 12% of the random population can be expected to be atopic, and when Kjellman [*12,20*] used a strictly selected group of nonatopic children, he found ranges of 0.3 to 3.1 μL/mL total IgE at three months, 0.9 to 28.0 μL/mL at six months, then a drop to 0.7 to 8.1 μL/mL at nine months. Although he found levels greater than the mean for that age to be predictive of future atopic manifestations, the retrospective nature of this study renders interpretation difficult. The difference in mean age between the groups in this study also exacerbates the problem.
2. While the RAST technique is sensitive, it is very possible that in infants with total IgE values of 10 μL/mL, even assuming that the majority of the antibody was directed to one of the allergens studied, the RAST technique would not indicate sensitivity.

In conclusion, we were unable to show in victims of SIDS any significant elevation of total IgE, nor IgE specific to allergens common to an infant's environment in Wayne County, MI. We concur with Clark et al [*9*] and suggest that our data do not support a hypothesis that anaphylaxis to milk proteins, dust, dust mites, or mold, mediated by IgE, is a factor in Sudden Infant Death Syndrome.

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