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Case Report

Immune biomarkers as an adjunct diagnostic modality of infection in cases of sudden and unexpected death in infancy (SUDI) at Tygerberg Medico-legal Mortuary, Cape Town, South Africa

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ABSTRACT

Child mortality is a major health concern worldwide with over 4.2 million infants dying before reaching the age of one year in 2016 alone. Several international intervention initiatives have resulted in a decrease in the number of infant deaths; however, the incidence of sudden unexpected death in infancy (SUDI) and sudden infant death syndrome (SIDS) remain unacceptably high. SIDS still accounts for approximately 50–80% of SUDI cases, followed by infection.

The aim of this study was to investigate a selection of immune biomarkers that are associated with an immune response in an effort to support the diagnosis of an infectious cause *("Infection")* e.g. bronchopneumonia, interstitial pneumonitis, etc., instead of *SIDS* in SUDI cases. C-reactive protein and 18 different cytokines were retrospectively quantified in serum collected during post-mortem investigations of SUDI cases admitted to the Tygerberg Medico-legal Mortuary in the Western Cape Province of South Africa between 2015 and 2017. Statistical comparison was done between infants with a final cause of death (COD) of *Infection* and *SIDS* to investigate any correlations between the immune markers and sociodemographic information of the groups. A p-value of < 0.0026, after Bonferroni correction for multiple comparisons, was considered as statistically significant.

A total of 169 cases were included, of which 65 (38.5%) were assigned a cause of death of *Infection* and 104 (61.5%) *SIDS* by forensic pathologists. The male to female ratio of the entire group was 1:0.97 and the median age at the time of death was 9 (interquartile range [IQR] 10.9) weeks. The majority (56.8%) of deaths occurred during the colder seasons (autumn and winter) and the median post-mortem interval was 4 (IQR 3) days.

No statistically significant differences were demonstrated for gender, season, sleeping position or bed-sharing between the *Infection* and *SIDS* groups. Age and interleukin-1α were identified as predictors of a COD of *Infection* before adjusting for the multiple comparisons problem. C-reactive protein was a statistically significant predictor of a COD of *Infection* even after adjusting for the effect of multiple comparisons.

The COD is primarily based on histopathology of the lungs, where other causes of interstitial inflammation have been ruled out, and where there are morphological changes present suggestive of infection, but not enough evidence to assign a final COD of *Infection*, the cases are concluded as *SIDS*. These biomarkers can therefore be valuable in the investigation protocol of SUDI cases to increase the number *Infection* cases where the histopathology of the lungs is suggestive of, but does not support conclusive evidence of infection.

1. Introduction

Sudden unexpected death in infancy (SUDI), where no cause of death (COD) is apparent, includes all infants who die unexpectedly under the age of one year, where fatal injury can be excluded before any investigations had been done to find a COD. A diagnosis of sudden infant death syndrome (SIDS) is made when the COD remains unexplained after a thorough medico-legal investigation (i.e. complete autopsy, review of clinical history and in-depth death scene investigation) [18]. Globally, SIDS is still confirmed to be the COD for up to 80% of SUDI

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cases [17,20] and although exact figures for South Africa are extremely scarce, Cape Town has been reported to have one of the highest SIDS rates in the world, with an incidence of up to 3.41/1 000 live births depending on the population group [7,25].

Several risk factors have been confirmed for SIDS and cases without risk factors are fairly uncommon [16]. The Triple Risk Model [8] describes the highest risk for SUDI in infants with latent biological vulnerabilities (e.g. prematurity, low birth weight, etc.), exposed to external threats or stressors (e.g. sleeping position, exposure to harmful substances, viral or bacterial infection, etc.) during a critical development period (e.g. young age).

Risks associated with SUDI include both sociodemographic (e.g. poor antenatal care, prematurity, low birth weight, young mothers with limited education, low socioeconomic status, colder seasons, male gender, a family history of SUDI, etc.) and modifiable factors (exposure to cigarette smoke, maternal drug and alcohol use, sleep-related factors, etc.) [5,12,17,26].

Despite several campaigns to modify the sleeping environment and educate parents about appropriate immunizations and infant care [4] the incidence of SUDI remains unacceptably high. Bed-sharing between infant(s) and adult(s) is still common practice in many populations [7] and although it promotes the spirit of *Ubuntu* (an indigenous African culture of universal human interdependence, solidarity and communalism) [11], it also increases the risk for SUDI. Prone sleeping is associated with thermal stress, possible airway compression or collapse and re-breathing of exhaled gases [6,13]. It also enhances ingestion or inhalation of bacteria on contaminated sleeping surfaces, such as mattresses, beds, sofas, etc. [14].

Antemortem respiratory infection symptomatology is common in cases of SIDS. Correspondingly, respiratory inflammatory changes are also quite often present in SIDS cases. Despite this, it has to be conceded that the degree of inflammatory change in the lungs as an indicator for pathology in SIDS deaths remain controversial [19]. Furthermore, pulmonary interstitial inflammation is by no means indicative solely of the presence of an infective agent in the lungs. The list of causes of interstitial inflammation/pneumonitis in infants is extensive, and forensic pathologists must carefully consider all information in a case to try to exclude other, non-infective causes of interstitial pneumonitis, before concluding that the COD is most likely an infection of the lungs. This includes, but is not limited to a detailed scene investigation, parental interview, environmental analysis and ancillary tests at autopsy. It is by no means an exact science.

Respiratory and cardiovascular disorders specific to the perinatal period, followed by Influenza and pneumonia have consistently been found to represent the leading cause for all infant deaths in South Africa [30]. Feedback mechanisms in the South African Forensic Pathology Service are often found lacking for various reasons – the vast size of pathology office drainage areas, lack of telecommunication methods, etc., so the Forensic Pathologist often does not have the privilege of repeated contact with the parents of a deceased child. It is therefore of crucial importance, in the interest of health impact strategies, and the clear and succinct communication of the COD to bereaved parents, for the forensic pathologist to categorize infection-related deaths clearly and as early in the examination of the case as possible, based on the findings.

Respiratory tract infections often present with blocked nasal passages, swollen mucous membranes, fever and increased oropharyngeal temperatures. This creates an ideal environment for *Staphylococcus aureus, Escherichia coli* and clostridia colonization, resulting in the release of staphylococcal and other interferon (IFN)-γ stimulating bacterial toxins [2,16,33]. Respiratory tract colonization by coliforms can increase the risk of SUDI by as much as 29 times. Viral and bacterial co-infections also dramatically exacerbate the clinical effect, with non-pathogenic commensal organisms being suspected of having a lethal effect in a susceptible infant [14].

Lower respiratory tract infections in infants are less common than upper respiratory tract infections, but have a higher morbidity and mortality [21]. Inflammatory changes in both upper and lower respiratory tracts of SUDI cases are often found during the post-mortem investigations and symptoms suggestive of respiratory infection in the days preceding death are commonly reported [2,12].

Different viruses have been detected in the respiratory tract of SUDI cases, but the presence or severity of clinical symptoms cannot be associated with a specific virus. Asymptomatic viruses may cause minimal clinical manifestations in infants, but it can lead to unregulated expression of inflammatory mediators, or a "cytokine storm" that might lead to sudden death [2,23,28].

Cytokines can be regarded as useful biomarkers of infection because it represents an early component of the host response to the presence of infection [9]. When the homeostasis of the body is disturbed, e.g. as a result of an infection, the release of acute phase proteins triggers a non-specific innate response, followed by the production and release of pro-inflammatory cytokines at the site of infection or injury and activation of the vascular system and inflammatory cells [15]. Immune dysregulation also increases the vulnerability of an infant and significant associations have been described between SUDI cases and polymorphisms of the regulatory genes of the immune system, such as interleukin (IL)-1α, IL-6, IL-10, tumour necrosis factor (TNF)-α and IFN-γ [14,16]. These and other cytokines have been correlated with lung damage and clinical outcome, and the balance between pro- and anti-inflammatory cytokines is important in immune modulation and the resolution of upper and lower respiratory tract infections [9]. IL-6 production is stimulated by the presence of bacteria and viruses, which induces fever and may affect the respiration of infants, increasing the frequency of apnoea. Inhibition of pro-inflammatory cytokines by IL-10 may clinically lead to hypoxaemia, hypoxia and ultimately death. However, IL-10 production can be inhibited by environmental factors, such as smoking, where nicotine can interfere with normal autoresuscitation after apnoea. The risk for SUDI is dramatically increased if this is accompanied by increased IL-1β production as part of an inflammatory response [33].

C-reactive protein (CRP) is an acute phase protein commonly used as a non-specific biomarker of infection and inflammation. It has been shown to be a valuable marker of infection in post-mortem samples [3,10,24,27]. However, very few studies have investigated any immune biomarkers as indicators of infection in SUDI and SIDS cases [34].

This study compared levels of specific immune biomarkers of inflammation in SUDI cases with a final COD of *Infection* and *SIDS*. Individual or combinations of biomarkers were also evaluated as possible predictors of infection to supplement histopathological analysis of the lungs in SUDI cases in order to assign a final COD.

2. Materials and methods

The Health Research Ethics Committee of Stellenbosch University approved the study before sample collection commenced (number N12/02/007). Anonymity and confidentiality were ensured by de-identification and only using the death register and unique study numbers of the cases. A waiver of consent was granted for this study, as collection, analysis and storage of specimens were performed according to the procedures set out in the Inquests and Criminal Procedures Acts (58 of 1959 and 51 of 1977 respectively).

A total of 169 cases admitted to Tygerberg Medico-legal Mortuary between 2015 and 2017 were included. All cases fit the criteria for SUDI (i.e. infants aged between seven days and one year who died suddenly and unexpectedly without a pre-existing medical condition or apparent cause). Blood was directly collected from the heart during the autopsy, centrifuged to separate the serum from the red blood cells and stored at −80 °C until the day of analysis.

A customized ProcartaPlex™ Multiplex Immunoassay was used to quantify IL-1α , IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL-18, IL-23, IFN-α , IFN-γ, macrophage inflammatory protein (MIP)-1α , MIP-1β, TNF-α and IFN-γ induced protein (IP)-10 (pg/ml). Standards and

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samples were analyzed in duplicate and results were interpreted with the ProcartaPlex™ Analyst Software.

DRG® CRP High Sensitivity and Elabscience® Human ELISA kits were used to quantify CRP and IL-10 respectively (pg/ml). All samples were analyzed in duplicate according to the manufacturers' instructions.

Tissue sections from the lungs were collected, processed and stained with haematoxylin and eosin (H&E) to facilitate histologic evaluation with light microscopy. A variety of characteristics, including oedema, congestion, interstitial pneumonitis, bronchopneumonia, focal collapse, the presence of formalin or iron pigment, alveolar debris, alveolar haemorrhage and bronchiolitis were noted for each slide. Interstitial pneumonitis of grade 3 (moderate: diffuse involvement and associated with interstitial oedema), and higher [19] was considered supportive of a final COD of *Infection,* where other causes of interstitial pneumonitis were ruled out as far as possible (Fig. 1).

As part of the medico-legal investigation, a questionnaire was completed by the parents or caregivers at the time the infant is admitted to the Tygerberg Medico-legal Mortuary. Sociodemographic details, clinical history of the infant and known risk factors for SUDI were captured.

Logistic regression model was fitted to investigate associations between the COD and immune biomarkers, as well as specific sociodemographic risk factors according to the literature. A p-value of <0.0026, after Bonferroni correction for multiple comparisons, was considered as statistically significant.

3. Results

The study group comprised a male to female ratio of 1:0.97 with a median age at the time of death of 9 (interquartile range [IQR] (5.55, 16.425)) weeks. The *Infection* and *SIDS* subgroups included 65 (38.5%) and 104 (61.5%) cases respectively. Overall, the majority (56.8%) of deaths occurred during the colder seasons (autumn and winter) and the median post-mortem interval (PMI) was 4 (IQR (3, 6)) days.

Details on the sleeping position of the infants were recorded for 146 of the 169 cases. Despite several awareness campaigns on the dangers of the prone sleeping position, the majority still slept on their stomachs or sides (44.5% and 47.3% respectively). Information on bed-sharing was available in 150 cases and the vast majority (95.3%) confirmed bed-sharing between the infant and other family members. Informal housing, as defined as a structure built with scrap material or small dwellings which house more than 10 people [7] was reported in more than half of the study group (55.9%).

The presence of clinical symptoms prior to death was positively associated with sleeping position, bed-sharing, ventilation and housing.

Younger age was significantly associated with the *Infection* group and can be regarded as a predictor for *Infection* ($p = 0.012$), before adjusting for effect of other confounders. Although marginally more males than females presented as SUDI during the study period, no significant differences could be demonstrated between gender and any of the variables.

4. Immune markers

All immune marker results were reported in pg/ml. In the crude analysis, statistically higher IL-1RA levels were found in cases during the warmer season compared to the colder season ($p < 0.0001$). IL-1α and CRP levels were significantly higher in the *Infection* than *SIDS* groups ($p = 0.028$ and 0.001 respectively), while IL-2 and IL-4 levels were significantly lower in the *Infection* than *SIDS* groups ($p = 0.009$ and 0.039 respectively). An increase of 1 pg/ml in CRP and IL-1α levels decreased the odds of COD of *Infection* by 11.2% and 0.8%, compared to *SIDS* groups respectively. An increase of 1 pg/ml in IL-2 and IL-4 levels increased the odds of COD of *Infection* by 0.2% and 0.8%, compared to *SIDS* groups respectively. No other statistical significance could be demonstrated between COD and any of the biomarkers (Table 1).

CRP levels was significantly higher in the *Infection* than *SIDS* groups ($p = 0.001$, after adjusting for multiple comparisons).

5. Discussion

Male gender has consistently been reported as a risk factor for SUDI. An extensive review of infant deaths between 1968 and 2010 from data released by the Centre for Disease Control and Prevention (CDC) also

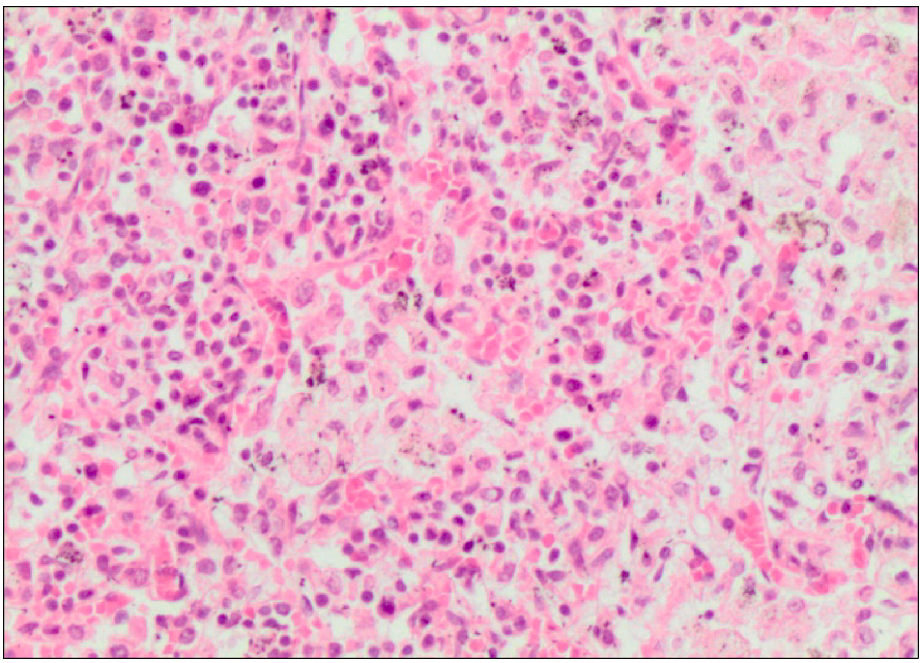

Fig. 1. Haematoxylin and eosin stained lung tissue displaying Grade 3 interstitial pneumonitis (200x magnification) with thickening of the alveolar walls and areas of alveolar collapse, as well as a thickened and hypercellular interstitium. The interstitium is expanded by mononuclear inflammatory cells, such as lymphocytes or macrophages.

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Table 1
Comparison of immune biomarkers and cause of death.

Biomarker	Cause of Death (n)		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*	p-value
	Infection	SIDS			
IL-1α	56	78	0.990 (0.983, 0.998)	0.992 (0.985, 0.999)	0.028
IL-1β	40	81	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	0.734
IL-1RA	41	82	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	0.051
IL-2	62	102	1.000 (1.000, 1.001)	1.002 (1.001, 1.003)	0.009
IL-4	41	81	1.002 (0.998, 1.006)	1.008 (1.000, 1.015)	0.039
IL-5	62	100	1.001 (0.943, 1.062)	1.033 (0.964, 1.108)	0.360
IL-6	62	100	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	0.735
IL-8	62	103	1.000 (0.999, 1.000)	1.000 (0.999, 1.000)	0.377
IL-10	62	100	0.973 (0.936, 1.013)	0.958 (0.906, 1.013)	0.131
IL-12	41	78	1.001 (0.999, 1.002)	1.002 (1.000, 1.005)	0.074
IL-18	62	103	1.000 (0.999, 1.000)	1.000 (0.999, 1.001)	0.748
IL-23	42	82	1.000 (1.000, 1.000)	1.000 (1.000, 1.001)	0.528
IFN-α	21	21	0.990 (0.969, 1.013)	0.984 (0.961, 1.007)	0.167
IFN-γ	62	100	1.000 (1.000, 1.001)	1.001 (1.000, 1.001)	0.107
MIP-1α	21	21	0.964 (0.908, 1.023)	0.955 (0.8921, 1.023)	0.191
MIP-1β	21	21	0.982 (0.943, 1.022)	0.981 (0.936, 1.027)	0.413
TNF-α	62	103	0.995 (0.986, 1.004)	1.001 (0.991, 1.012)	0.800
IP-10	62	103	0.997 (0.997, 1.000)	0.999 (0.997, 1.000)	0.065
CRP	64	103	0.880 (0.823, 0.941)	0.888 (0.8263, 0.954)	0.001

*Adjusted for effects of gender, season and age.

showed a male predominance of 60% and 61% in cases of acute respiratory infections and respiratory distress syndrome respectively [22]. However, statistical analysis in the current study did not demonstrate any significance for gender, and in fact found a lower percentage of males in the *Infection* group than *SIDS* (45% and 55% respectively). Previous SUDI studies at the Tygerberg Medico-legal Mortuary have also produced variation in male-to-female ratios over time (data not shown) and it is postulated that sociodemographic and other factors, such as temperature, rainfall, access to water and sanitation, the presence of co-morbidities, etc. could contribute towards these discrepancies.

SUDI is a multifactorial phenomenon and it is clear that infection is one of the major contributors. Acute phase reaction to infection is characterized by IL-1β and IL-6 production, followed by CRP synthesis in the liver and release into the circulation. CRP starts increasing within 6 h of the onset of infection, reaches a peak around 48 h post-infection [10] but can remain increased for up to 6 days after death [32].

As expected, CRP and IL-1α were significantly increased in the *Infection* group as a result of an immune response possibly due to viral or bacterial infection. However, IL-6 levels in this group were increased, but not significantly different from the *SIDS* group. It is unlikely that this was due to the PMI, because it was well within the reported period of stability [32]. Although these are non-specific markers which cannot identify the exact causative pathogen or location, it can confirm the presence of infection [3,10].

The association between season and cytokine expression is an evolving field. While environmental and host factors have been reported to affect the immune response in healthy adults, very little is known in infants. It is also possible that variation in cytokine expression can be associated with known seasonality of infectious diseases, e.g. influenza [1,29,31]. Although this study identified a significant seasonal association in IL-1RA expression, the clinical, pathological and physiological relevance is not clear. The small sample size also does not allow for extrapolation to the general paediatric and / or SUDI populations.

In the Western Cape Province of South Africa, the Tygerberg Medico-legal Mortuary institutional protocol and Department of Health budget does not provide for molecular identification of specific viruses, mainly due to the high cost involved in these tests. The gold standard for diagnosing an infection in SUDI cases remains histological evaluation and in many cases there is suggestive, but inconclusive evidence to confirm *Infection* as the final COD. These cases are regarded as *Borderline SIDS* and then assigned a final COD of *SIDS*. However, if the levels of biomarkers indicative of inflammation, such as CRP, IL-1α and IL-6, are increased in these borderline cases where moderate histological changes are present, it could provide more conclusive evidence of infection and the COD could be amended to *Infection* rather than *SIDS*.

6. Conclusion

This study did not include any analysis to identify specific viral or bacterial infections, but CRP, IL-1α and IL-6 were useful biomarkers to suggest infection in the absence of discriminatory tests. It can be valuable if used in combination with histological analysis to increase the number of cases in the presence of infection to be correctly classified as *Infection*.

However, not all the information was available for all the cases due to incomplete questionnaires, and this data could be subject to recall bias.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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