SCIENCE DIGEST

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Occupational health issues experience by embryologists

Health data from the UK indicated that the most common work-related ill health issues were stress, depression, anxiety and musculoskeletal problems. In addition health and social work professions had significantly higher rates of work-related illness than many other industries. In response to these data, the UK Association of Reproductive and Clinical Scientists (ARCS) undertook a workforce survey to determine what occupational health issues were being experienced by the profession (1). The survey only included those employed as embryologists employed in 80 different licenced fertility treatment centres plus six from overseas centres. Over half of the 62.2% respondents had 10 or more years experience. In summary, 43.5% had musculoskeletal problems relating to static positions and repetitive actions. Stress and mental health problems were identified in 27.8% of respondents frequently associated with high work demands and low work autonomy. Ocular problems in 12.2% were associated with microscopy work in clean rooms and auditory problems (3.6%) were associated with workplace noise. Needlestick injuries (3.1%) were associated with mental health problems presumably related to the transmission of infectious diseases and liquid nitrogen related injuries were reported in 3.1% of respondents. Overall the survey concluded that embryologists experienced a number of occupational health problems of which musculoskeletal and mental health and work stress issues were the dominate issues emerging from the survey which appeared to be linked to lack of control of workflow and irregular breaks as well as workplace stress.

Proof of innocence by next generation sequencing?

Sometimes what appears to be the obvious is not proof of effect or guilt. In 2003 an Australian woman was convicted of killing her four children aged between 19 days to 18 months over a 10 -year period. All four died in their sleep and the woman was sentenced to 30 years imprisonment. No clear motive for all the murders was established and there was no history of child abuse. Importantly, at the times of the children's deaths there was no evidence of asphyxiation, at least two died from cardiac arrest and the conviction was based on circumstantial evidence. At the time of the trail reference was made to "Meadow's Law" despite it being discredited as having no basis in fact i.e. the paediatrician made it up! In 2020 a judicial enquiry was launched to consider the quality of the medical evidence provided at the original trial and as part of the enquiry next generation sequencing (NGS) was undertaken on the mothers and children's stored DNA (the father refused to give a sample). The investigators initially looked at genes known to be associated with sudden infant death but expanded the search to genes associated with sudden unexpected death (SUD). The mother was identified as having a rare (often lethal) variant in the calmodulin 2 gene associated with myocardial malfunction, which has been associated with SUD and is known to have incomplete penetrance. The pathogenic variant was identified in her two daughters and could account for a natural death. The two sons were identified as compound heterozygotes for a rare missense mutations associated with lethal epilepsy in mice but unreported in humans, and one of the sons was an epileptic and blind. The authors of the publication (2) who collaborated internationally to investigate this case, conclude that NGS and WGS are necessary and justified to identify cases of sudden unexplained deaths in infants. Currently the mother is still serving the sentence and a petition signed by 90 scientists, medical practitioners and related health professionals indicating the mutations could have caused the infant deaths has been presented to the review.

N95 masks and cardiorespiratory function

The advent of the SARS-Cov-2 (COVID-19) pandemic brought about the almost universal wearing of face masks with an ensuing debate of which mask was best. Generally the N95 mask was acknowledged as the most likely face mask to provide optimal protection. In a recently published report, researchers from China have investigated the effects of surgical and N95 masks may have when exercising (3). Three groups of volunteers with normal BMI were divided into no masks, surgical masks and N95 masks. The volunteers then underwent cardiopulmonary exercise testing (CPET). The outcome of this research was that both masks were associated with shortness of breath with the N95 masks having a more negative impact on ability to perform exercise. N95 masks in particular were associated with carbon dioxide retention, a reduction in exercise tolerance, lower breathing frequency and a lower ventilation efficiency. Although surgical masks demonstrated a similar trend it was not as significant as the N95 masks. The authors conclude that both mask types have a negative impact on cardiopulmonary function but the effect was greater with N95 masks and caution about wearing either mask when exercising.

Is it just *BRCA1* and *BRCA2* we should be concerned about in breast cancer?

It is well established that both *BRCA1* and *BRCA2* are important in hereditary breast cancer and it is now well established that approximately 10% of patients with breast cancer carry a predisposing germ-line mutation. Although *BRCA1* and *BRCA2* are both the first described and best known breast cancer genes, and are linked to the most hereditary risk for breast cancer, there are other genes that are linked to breast cancer. Until now these have been difficult to describe but with the ability to sequence multiple genes in a single assay decisions will have to be made on which genes should be identified as being responsible for susceptibility to breast cancer. Recently two high quality major studies (4,5) have identified a number of genes that are statistically associated with breast cancer risk. The Breast Cancer Association Consortium (BCAC) involved 60,466 breast cancer patients and 53,461 control patients from 44 international sites and sequenced 34 genes known or suspected to be causing breast cancer. The second study, Cancer Risk Estimates Relating to Susceptibility Consortium (CARRIERS), sequenced 37 cancer related genes. Detailed statistical analysis of the resulting data was undertaken in both studies. The major findings were that nine genes were statistically associated with breast cancer and across both studies *ATM, BRCA1, BRCA2, PALB2* and *CHEK2* had the highest penetrance for causing breast cancer and possibly *TP53,* although the latter was just below the significant cut-off. Discussion concerned the position of laboratories when testing for breast cancer susceptibility genes and whether a single pan-cancer panel was the better option rather than testing for single genes. An additional factor related to some of the genes had variable penetrance for breast cancer but may be significant for ovarian cancer raising the question of how well the functions of the identified 'risk' genes are understood.

A new method for malaria testing

Malaria is a life-threatening disease and is at times difficult to diagnose. The use of the thick blood film and microscopic examination is still the most common method for malarial parasite identification. However, despite the relative ease of establishing this technique, it requires significant skill especially in identifying the different malarial parasites, particularly when a mixed infection may occur. Newer techniques such as immunochromatography may be affected by malarial parasite density and suffer from lack of high sensitivity.

More recently the use of PCR techniques have emerged and are showing potential especially for low malarial parasite numbers. In a recent publication from China (6) the researchers undertook the use of digital PCR (dPCR) as a new technique for the detection of malaria using all four main *Plasmodium* species: *P. vivax, P. falciparum, P. ovale* and *P. malariae.* Using blood from 29 patients with known malaria infections, 20 with fever (but not malaria), 20 healthy controls and six patients with other parasitic infections. Of the malaria patients 22 had *P. falciparum*, 6 *P. ovale,* 4 *P. vivax* and 4 *P. malariae.* Using dPCR the researchers were able to distinguish all four types of malaria species simulttaneously. Using the two sets of control data it was established that the dPCR technique had a sensitivity of 98% and a specificity of 100% and was able to distinguish mixed infections. The authors conclude that the new technique is both rapid and accurate for the diagnosis of malaria and can be used on stored blood samples.

Genomic autopsies and pregnancy loss and perinatal death

Despite the advances in maternal and fetal care in developed countries eight fetal and neonatal deaths occur in Australia every day. Frequently the cause or uncertainty about these deaths creates significant issue for future pregnancies. While many of these deaths are investigated less than 50% have an autopsy performed. While congenital abnormalities can account for approximately one-third of the deaths the underlying cause of many of such abnormalities is not determined, which limits the ability for counselling for future pregnancies. Currently approximately 70% of congenital abnormalities related deaths are unexplained. In the present publication (7) an international collaboration by researchers from Australia, Turkey, Spain, and the USA offered genomic autopsy using exome sequencing or genome sequencing. Using samples obtained from the parents and those retained at routine autopsy from the child and the placenta all samples underwent microarray analysis. A total of 200 consecutively referred families were included in the current publication. Genomic sequencing was undertaken and sequence mapping, variant calling was undertaken. Analysis and interpretation was in two stages, to identify mendelian related disease variants and the second to identify potential disease variants in novel genes. RNA analysis was also undertaken to identify any splice variants. A total of 105 families were able to receive a definitive or candidate genetic diagnosis. These were either an autosomal recessive (30.8%), X-linked recessive (3.8%) or autosomal dominant (7.7%) with a risk of recurrence. These data informed some families to use preimplantation or prenatal diagnosis for future pregnancies. The authors propose that the use of genomic autopsies improves the standard of care and enhances families options where fetal or neonatal death occurs.

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