UK centres are not following the Royal College of Pathologists’ recommendations for storage of Guthrie cards: a national policy is needed

Stored neonatal blood spots are a valuable source of DNA for retrospective diagnosis. A recent working party of the Royal College of Pathologists recommended storage of neonatal screening test (Guthrie) cards for at least 20 years provided that no deterioration of the sample has occurred. Our recent attempts to trace such cards convince us that a UK national policy and central funding for storage of Guthrie cards is necessary.

Mitochondrial encephalopathy with stroke-like episodes (MELAS) is frequently associated with a mitochondrial DNA point mutation A3243G. Segregation and proliferation of this mutation in different tissues (ECMC) is not well understood. Levels of the 3243 mutant in blood are usually lower than in muscle and cross sectional data suggest that the level of mutant DNA may fall with increasing age. There is concern that cases of MELAS may be missed if diagnosed using the polymerase chain reaction (PCR) on blood. Longitudinal studies are necessary to clarify this issue. We have commenced a European collaborative study using Guthrie cards to compare levels of the 3243 mutant mtDNA in blood at birth and during diagnosis, under the auspices of the European Neuromuscular Centre.

We recorded 70 patients with MELAS born in the UK after 1970, and with the informed consent of the patients or parents or both as appropriate, sought their Guthrie cards and interview data. A telephone survey of the 25 UK neonatal screening laboratories showed marked variability in practice between regions. Two centres use serum for screening rather than blood spots, and one stores blood spots for five months only. Only 12 centres store cards for longer than 10 years, and the trend is towards shorter periods because of financial pressures. We suggest that a national policy for storage of neonatal blood spots is needed and that this may require central funding. Centralisation of cards and records would be an advantage as families now move between regions frequently and do not always recall the information in their previous addresses. Cards should be stored in such a way as to prevent cross contamination, particularly if PCR is to be used in analysis of the blood spot.

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Cyclopia and sirenemia in a liveborn infant

Recently, Chen et al. published the case of a stillborn infant who presented with cebocephaly, acetyl-CoA dehydrogenase (MCAD) deficiency and concurrent triglyceride levels. The authors inferred that the MCAD deficiency was the cause of the triglyceride levels.

In 1992, we participated in an epidemiological study in an international collaboration, providing data from the EECM to the study. A paper has not been published as there are difficulties in arriving at the correct title. In 1994, in a letter to the Editor, we commented that we had observed a case with cyclopia and sirenemia that may be a clinical representation of the syndrome described by Kallén et al. in a liveborn infant.

The infant was the product of the second pregnancy of a 29 year old mother and a non-consanguineous 33 year old father, both healthy. There was no family history of congenital malformations. The first pregnancy ended, a year earlier, in a normal male infant. In 1978, the proband was born spontaneously at 39 weeks of a non-terminated pregnancy, apart from a respiratory tract infection during the first 15 days of gestation. The mother denied any exposure to known teratogens, including alcohol and tobacco. She also denied having had problems in conceiving. At birth, the infant’s weight was 1600 g (<3rd centile). The infant died at 15 minutes and had microcephaly, absent nose with presence of a proboscis, cyclops, sirenemia, and a clinical right forebrain deficiency. No external genitalia or anus were visible. The umbilical cord contained only an artery and a vein. It was not possible to perform any radiological study, karyotype, or necropsy.

The prevalence of any type of holoprosencephaly in the series of 1 245 863 births monitored by the EECM between 1980 and 1996 is 0.83 per 10 000 births, while the prevalence of cyclopia and sirenemia is 0.10 and 0.08 per 10 000 births, respectively. In an epidemiological study on the association of holoprosencephaly and caudal dysgenesis, it was observed that both types of abnormality tend to be preferentially associated. That is, both are associated in the same child with a frequency that is significantly higher than would be expected just by chance. However, the combination of the two most extreme forms of alteration of the cephalic and caudal part of the embryo, cyclops and sirenemia, is very infrequent. In fact, our case was identified among a total of 1 245 863 births and appears that this is the first case published with cyclopia and sirenemia, bringing to three the total published cases with different degrees of holoprosencephaly and sirenemia.

Cyclopia and sirenemia are gross alterations of early blastogenesis. Thus, as Opitz postulated and we reported, the combination of the two conditions, which is lethal, is a polytopic response of the alteration of the primary field, mostly affecting the midline. We have also observed that mothers of infants with blastogenic defects have a higher proportion of previous abortions that may mask the recurrence risk. However, we consider that in cases of holoprosencephaly (with different degrees of severity) and sirenemia, in the absence of abnormalities and maternal diabetes, the recurrence risk at birth should be very low.

We think that it is important to present this case in detail since, at present, it is the only one that has the two most severe forms of alteration of the cephalic and caudal part of the embryo (cyclops and sirenemia), and also because it was identified among a series of consecutive births, which allows the estimation of the birth prevalence of this entity.

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1 Chen CP, Shih SL, Liu FF, Jan SW. Cebop-cephaly, alobar holoprosencephaly, spina bifida -
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It is a salutary experience to open the index of a history book and find oneself cited (albeit only once, and then only in parenthesis), if for no other reason than that it reinforces one's awareness of the passage of time. The events related in Errol Friedberg's book took place within living memory and the author deserves credit for eliciting for us the accounts of those who were responsible for them. The discoveries themselves are, of course, fascinating. While the need for living things to have means of dealing with the chemical and physical threats to their genomes is old hat to us, and the ways in which they achieve genomic stability and fidelity are not conceptually difficult today, this was not the case in the early days of DNA repair. It was first necessary to know the gene's composition, its structure (established by Dan Brown and Lord Alexander Todd in 1952), and its conformation (as shown by Watson, Crick, and Wilkins in 1954). Indeed there is a subtext to the story in that the giants in the field of molecular genetics (as it came to be known) were in general little interested in genomic repair and tended to regard such work as second-rate, largely because it was often done in national laboratories established and maintained for the purposes of supporting atomic energy and weapons research. Yet DNA repair has contributed more than its fair share of major discoveries, excision repair, mismatch repair, and the SOS coordinated inducible response being the most exciting with implications that extend to modern clinical medicine. Even the classic work of Avery, McLeod, and McCarty in 1944 showing that genes are made of DNA was antedated by Hollaender and Emmons in 1941, who showed clearly that the wavelength of ultraviolet light that was most effective in inducing changes in genes coincided with the peak of absorption by nucleic acid.

Various controversies are dealt with as fairly as appears possible. It is understandable that Friedberg has no wish to disturb the amicable relations that he has with his colleagues. One senses, however, that there could be another even more entertaining history written that gave more prominence to the paranoia, suspicions, and personal animosities of the characters who pandered them "warts and all".

While the field up to, say, 1970 is covered well, after that the coverage is selective. There is, for example, no more than a paragraph about the repair of ionising radiation induced double strand DNA breaks, despite the fact that the field is of major importance, and the commonality of mechanism with immunoglobulin gene rearrangement foreseen since around 1980 has been spectacularly demonstrated in the last few years. Although there is a full and almost complete discussion of the inducible SOS system (lacking only an acknowledgement of the contribution of Peter Emmerson in Newcastle), there is no account of the discovery of the molecular mechanism by which mutations are made by the SOS gene products. Obviously, a second and updated edition will be needed before Friedberg himself retires.

One final thought in the reviewer's mind concerns the conceptual nature of the really significant advances described in this book. They were frequently made by bright people thinking beyond the confines of their field, often beyond what they were being paid to do, going out of their way to interact with other bright people who were needed for mental cross fertilisation. The advances were more often than not predictable only with hindsight. Rarely would they have been the subject of a successful grant application in today's world.

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Cyclopia and sirenomelia in a liveborn infant.

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