

Meconium analysis has an added advantage in that exposure to the toxicants may occur only in small amounts but repeatedly over prolonged periods. Thus, the analysis of a cumulative, repository matrix (meconium) compared to an acute phase matrix (blood), may be more sensitive in detecting such types of exposure. Furthermore, meconium represents fetal tissue and is therefore a direct measure of fetal exposure to the toxicant compared to maternal blood or maternal hair. The latter are indirect measures of fetal exposure and can be influenced by the metabolism of the drug/compound by the mother as well as by factors that affect placental transfer of the compounds.

Different methods have been used to analyse neurotoxicants in meconium, although GC-MS (gas chromatography/mass spectrometry) provides the most sensitive and specific method of analysis.<sup>5</sup> However, strict criteria for the identity of compounds have to be used; otherwise the high specificity of the method will be compromised. Unless the molecular ions are detected in the mass spectrum, the presence of breakdown ion masses alone may not be sufficient for identity unless specific ratios of target ion to qualifiers are also required.

Whether meconium analysis can be used to determine the timing of xenobiotic exposure is a possibility that merits further investigation. Theoretically, since meconium is not normally excreted in utero, serial analysis of meconium may indicate periods of xenobiotic exposure during gestation. This concept has been explored with illicit drugs in animal and human studies. In a study of pregnant rats that were serially exposed to morphine or cocaine during gestation, the concentration of the drugs in the pups' meconium was significantly correlated to the timing, duration, and dose of cocaine or

morphine that were administered to the dams.<sup>8</sup> Similar relationships have also been clinically reported in infants born to mothers who have used cocaine and heroin during pregnancy.<sup>9 10</sup> However, extrapolation of this observation to neurotoxicants, specifically for the pesticides, may be premature at the moment since the toxicants may undergo different patterns of metabolism and distribution compared to the drugs of abuse. What is therefore needed is an animal model or human circumstance that can study such a relationship.

A major limitation of meconium analysis is that meconium is a more complex and difficult matrix to analyse compared to blood or urine. Meconium analysis requires a thorough, preliminary clean up procedures (e.g. solid phase extraction) prior to any analytical assays. This is a critical step, especially in GC-MS assays, where sensitivity and specificity are greatly influenced by background noise (matrix effects). As previously mentioned, the use of GC-MS for the analysis and identification of compounds in meconium must employ strict criteria for identification since many materials in meconium may co-elute with the compounds of interest.

Overall, meconium analysis is a sensitive and powerful technique to detect fetal exposure to xenobiotics, including neurotoxicants. The latter is important because the fetal brain is most vulnerable to the adverse effects of these compound due to its rapid state of brain growth and development during gestation. Thus, the sensitive detection of exposure and the amount of exposure can be helpful in our understanding of the immediate and long term effects of these compounds on the newborn infant and developing child.

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#### Newborn screening

## Newborn screening for congenital toxoplasmosis: feasible, but benefits are not established

R Gilbert, C Dezateux

Perspective on the paper by Schmidt *et al* (see page 661)

The report on the Danish newborn screening programme for congenital toxoplasmosis in this month's issue

adds to evidence from similar programmes across the globe that newborn screening is feasible.<sup>1–3</sup> Screening for

toxoplasma specific IgM antibodies in newborn dried blood spots was first offered in 1988 by the New England Neonatal Screening Program. Since then, newborn screening programmes for congenital toxoplasmosis have been established in Denmark (in 1992),<sup>1</sup> Poznan, Poland (in 1994),<sup>4</sup> Porto Alegre, Brazil (in 1995),<sup>6</sup> and Campos dos Goytazaces, Brazil (in 1999).<sup>7</sup> In addition, screening studies have been conducted for a limited period in southern Sweden (1997–98)<sup>8</sup> and Ireland (2005–07).<sup>9</sup> The estimated birth prevalence of congenital toxoplasmosis per 10 000 live births reported by these programmes ranges from 0.7 in Sweden<sup>8</sup> and 0.8 in Massachusetts,<sup>3</sup> to 7.1 in Poland,<sup>4 10</sup> and in Brazil, 5.4 in the

private sector<sup>2</sup> and 20 in the public sector.<sup>7</sup> In European cohorts, approximately 10% of infected children have retinochoroiditis during infancy, rising to 16–18% by 4 years old.<sup>11–12</sup> Bilateral visual impairment is rare, affecting up to 4% of children with retinochoroiditis.<sup>13</sup> Screening detects between 43% and 85% of infected neonates.<sup>4–8–14–17</sup> The very low false positive rate means that the probability of congenital toxoplasmosis in screen positive infants is usually over 25%.<sup>1–2–4–8</sup>

Newborn screening offers an apparently attractive option for preventing sequelae from congenital toxoplasmosis. It costs about one tenth as much as antenatal screening and avoids the inconvenience of repeated testing during pregnancy, the risk associated with amniocentesis for prenatal diagnosis, prolonged antibiotic administration during pregnancy, and termination of fetuses at very low risk of disability.<sup>18–20</sup> However, far from encouraging adoption of newborn screening, the Danish report in this issue highlights the lack of evidence regarding the key criterion for screening programmes: the need for an effective treatment.<sup>1</sup>

Infants detected by newborn screening are prescribed treatment to prevent the occurrence of new retinochoroidal lesions after birth. Schmidt *et al* reported new lesions in only three of 55 infected children (5%) after 3 months of pyrimethamine–sulphonamide treatment. Whether more children would have developed new lesions if they had not been treated is not at all certain. There are no randomised treatment trials in infants and, in cohort studies, infected infants are almost always treated. One exception was a cohort study of antenatal screening in the Netherlands.<sup>21</sup> Paediatricians could not be persuaded to treat the 12 infected children, three of whom had retinochoroiditis and one had intracranial calcification. At 3 years, the rate of clinical manifestations did not differ significantly from children screened in France and Austria who were treated prenatally and for one year after birth, although the power to detect a difference was low.<sup>22</sup>

Evidence from randomised trials comparing anti-toxoplasma treatment with no treatment or placebo is limited to adults, most of whom would have acquired toxoplasmosis after birth.<sup>23</sup> All three trials were of poor quality. Two trials showed no evidence for a beneficial effect of treatment. The third, in Brazilian adults with frequently recurring disease, found that trimethoprim-sulphamethoxazole reduced the recurrence of retinochoroiditis.<sup>24</sup> As toxoplasmic retinochoroiditis is more frequent

and severe in Brazil than in Europe, possibly due to differences in parasite strain, these findings may not be generalisable to European infants with congenital toxoplasmosis.<sup>25–26</sup>

Indirect evidence for the effect of postnatal treatment on retinochoroiditis comes from cohort studies that examined the effect of prenatal treatment. No cohort studies have found that prenatal treatment significantly reduces retinochoroiditis in infected infants<sup>27</sup> or in children followed up to school age (unpublished data, EMSCOT study, personal communication, R Gilbert).<sup>11</sup> Prenatal treatment would be expected to have an impact on the risk of retinochoroiditis if it is given prior to encystment of the parasite. The lack of evidence for a reduction in lesions may be because treatment is usually given after cyst formation: transformation of the infective tachyzoite form of *Toxoplasma gondii* into the bradyzoite form is complete by two weeks after infection.<sup>28</sup> Bradyzoite cysts are impermeable to antibiotics but are thought to break down transiently when new retinochoroidal lesions develop.<sup>28–29</sup>

Uncertainty about the effectiveness of postnatal treatment is manifest by the diverse treatment regimens and in some centres, high rates of loss to follow up.<sup>27–30</sup> Depending on where congenital toxoplasmosis is diagnosed, postnatal prophylactic treatment can be given for three months (in Denmark), or, in some French centres, for two years.<sup>27</sup> Yet even in France, where women require a record of being offered prenatal screening for toxoplasmosis in order to qualify for state maternity benefits,<sup>31</sup> there is poor adherence to follow up in some centres,<sup>32</sup> and widely varying approaches to management.<sup>27–33–34</sup> Pyrimethamine–sulphonamide has been the mainstay of postnatal treatment but is associated with serious adverse effects (mainly neutropenia) in 14–50% of infants<sup>3–35</sup> (unpublished data, EMSCOT, R Gilbert). Alternative treatment options include spiramycin, co-trimoxazole, and azithromycin, but no comparative data exist.<sup>36</sup> Of further concern is evidence that the parents of children diagnosed with congenital toxoplasmosis are twice as likely to have high levels of anxiety when their child is 3–4 years old than are parents of uninfected children.<sup>37</sup> This is despite the finding that, on average, developmental, cognitive, and behavioural outcomes were similar in infected and uninfected children born to infected mothers.<sup>37</sup>

How should clinicians and policy makers proceed given the evidence that newborn screening is feasible, the lack of clear evidence of benefits, and the risk of harm? The first step is to

determine the burden of symptomatic disease due to congenital toxoplasmosis that might potentially be prevented by screening and treatment. Newborn screening studies can provide valuable information on the incidence of congenital toxoplasmosis and have been used for this purpose in Sweden, Poznan, Mexico, Denmark, Brazil, and most recently Ireland.<sup>2–5–8–9</sup> However, setting up a screening programme is costly and once running, it can be hard to stop. Other disadvantages include the need for long term follow up to determine outcomes, exposure of children to potential harmful effects of drugs, and lack of comparative information from untreated children. A less costly approach uses active clinical surveillance to identify newly diagnosed children with clinically suspected congenital toxoplasmosis seen by paediatricians, laboratories, or ophthalmologists. The findings of a UK-wide study between 2002 and 2004, published online,<sup>38</sup> estimate that approximately six children with neurological symptoms due to congenital toxoplasmosis will be born in the UK each year (700 000 births), 24 with signs of ocular or neurological disease. However, more ocular disease occurred in children that acquired toxoplasmosis after birth than in those who were infected congenitally; in adulthood, most ocular toxoplasmosis would be due to postnatally acquired infection.<sup>39–40</sup> These findings suggest that the public health focus should shift to primary prevention of postnatally acquired infection.

Another approach to determining the burden of disease is to test residual newborn screening dried blood spots. These have been widely used in other conditions either on an anonymised basis, or retrospectively by retrieving blood spots for children who are symptomatic, and have been shown to be a valuable resource for biomarkers of conditions manifest or detectable in early life. In the UK, codes of practice for their use have been established by the UK Newborn Screening Programme Centre (<http://www.newbornscreening-bloodspot.org.uk/>). The difficulty with this approach for toxoplasmosis is that additional samples from mother or child would be needed to confirm toxoplasmosis based on a single test of a newborn blood spot as the predictive value of the screening test is only about 25%. Attrition due to difficulties in tracing families, obtaining consent, and actually finding the blood spot card are additional obstacles and have limited the success of this approach to date. Storage conditions of the filter paper cards that contain the blood spots need to be optimal (about –20°C) in order to

maintain IgM sensitivity, which is particularly influenced by temperature (personal communication, Eskild Petersen).

The UK National Screening Committee has recommended that antenatal prenatal screening should not be introduced, in view of the lack of evidence for treatment effectiveness, clinical harms, costs, and difficulties in implementation.<sup>16</sup> Newborn screening has not been supported pending information on the effectiveness of postnatal treatment from a randomised controlled trial. Given the low risk of new lesions after birth, such a trial would need to be very large, involving several countries.<sup>13</sup> A trial of postnatal treatment may be more feasible in Brazil, or other tropical countries, where the birth prevalence of congenital toxoplasmosis and risk of clinical sequelae are higher. However, differences in the strain and virulence of the parasite are likely to mean its findings would be of limited relevance to Europe.

For the foreseeable future, decisions on whether to start, stop, or continue antenatal or newborn screening will be made in the context of considerable uncertainty, as the definitive treatment trials need to be large and will be extremely costly. Waiting for evidence that treatment does not work is untenable, as screening should always be based on positive evidence of benefit. Currently, there is no clear evidence that antenatal or neonatal screening is beneficial. Moreover, the fact that screening has been carried out for decades does not provide evidence of its value, but does reflect costs that will be incurred by stopping screening. To inform decisions now, clinical and cost effectiveness models can be used to combine existing evidence from cohort studies with regional estimates of the burden of disease to weigh the balance of potential benefits, harms, and cost effectiveness.<sup>41</sup> In addition, value of information models can be useful to estimate the cost effectiveness of further research, taking into account consequences such as continuing or dismantling established programmes.<sup>42</sup> Such analyses are important when very large and expensive trials are being considered and are particularly relevant to France and Austria, which operate centrally regulated antenatal screening programmes. In France, screening costs at least £50 million per year (for 780 000 births per annum).<sup>43</sup> A key principle is that policy makers need to decide whether to stop or continue screening independently of the laboratory services and clinicians that stand to gain from the programme. This can be difficult as the same laboratories may be needed to

provide the clinical data, and, as toxoplasmosis is relatively uncommon, to explain the disease and its management. In the UK, screening policies are reviewed and recommendations made by the National Screening Committee, an independent and internationally recognised group. This independence is vital, to ensure that testing is not implemented just because it can be done, but because there is good evidence to suggest that the benefits to pregnant women and their children outweigh the harms. Further studies are needed to address this point.

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R Gilbert and C Dezateux

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