Use of dried blood from the heel (Guthrie card) in the diagnosis of congenital enterovirus infection☆

Utilidad de la sangre seca del talón (tarjeta de Guthrie) en el diagnóstico de infección congénita por enterovirus

To the editor:

Enteroviruses (EVs) are among the most common viruses that cause disease in humans. In the United States, it is estimated that every year there are 10–15 million new infections, mainly in children and particularly in infants aged less than 1 year. These infections exhibit a seasonal pattern (spring and summer) and may be sporadic or occur in the context of an outbreak.[1]

Neonatal EV infections may be acquired prenatally (congenital or intrauterine), during delivery (vertical transmission) or postnatally (household or environment). The incidence of EV infections before 1 month post birth is approximately 12%, and 79% are asymptomatic, while 4% require hospital admission.[1] Some authors consider that detection of EV in the first 5–10 days post birth is indicative of congenital infection.[2,3]

Few studies have analysed the characteristics and epidemiology of congenital EV infections, and Abzug et al.[2] were the first to suggest that these infections could be associated with some form of congenital abnormality.

One of the main issues is the use of an appropriate diagnostic method. Reverse transcriptase polymerase chain reaction (RT-PCR) has become the gold standard for diagnosis of EV infections on account of its sensitivity and specificity. This technique may be applied to nearly any type of biological specimen.

To estimate the incidence of congenital infections by EV, we tested for the presence of the EV genome in heel stick/dried blood spot samples in patients with known EV infection (detection by RT-PCR) before 7 days post birth.

In the 2015–2019 period, we diagnosed 23 cases of EV infection in newborns aged less than 10 days through detection in throat swab or nasopharyngeal aspirate samples. All of them presented with fever of unknown origin, irritability and food refusal. The samples were analysed with a multiplex one-step real-time RT-PCR assay (Allplex RV, Seegene, South Korea) for detection of 16 different viruses, including EV.

We performed tests for detection of EV in the dried blood spot by extracting nucleic acids from the sample (EZ1 Advanced XL, Qiagen, Spain) followed by amplification with a commercial RT-PCR kit (FTD® Viral meningitis; Luxembourg).

Testing only detected the EV genome in the heel stick sample of 1 newborn (4.3%), which could be interpreted as evidence of congenital EV infection. This infant was brought to the emergency department with fever of unknown origin at 5 days post birth, and EV was first detected in a throat swab sample. The EV detected in this sample and the EV detected in the dried blood were identified as echovirus 30. We obtained throat swab samples from both parents and a vaginal swab from the mother, all of which tested negative for EV.

The possibility of detecting congenital EV infections was first explored by several research groups in Japan that used preserved umbilical cord samples. For instance, Morioka et al.[4] were able to prove intrauterine infection by echovirus 7 using this type of sample. In Japan and South Asian countries, a dried portion of the umbilical cord (UC) has to be preserved by law for a minimum of 5 years.[4,5]

In Europe, umbilical cords are not preserved routinely, so Smets et al.[6] were the first to report detection of a coxsackievirus B3 genome in a dried blood spot collected 4 days post birth in a newborn aged 17 days with fatal disseminated intravascular coagulopathy. Later on, Miyata and Saitoh[5] confirmed the detection of EV in the cord blood of a newborn aged 3 days with fever and in the stools of the mother, while test results for other newborns and environmental specimens were negative.

Thus, it appears that detection of EV in dried blood spots could be used to attempt to identify congenital infections by EV, as they are used for diagnosis of cytomegalovirus infection. In the case presented here, it is reasonable to conclude that detection in this type of sample is indicative of intrauterine infection, probably acquired by the mother in the last weeks of gestation. The percent positive obtained in our study is only a rough approximation derived from the small sample of tested newborns, and a large-scale multicentre study would be necessary to establish the actual incidence of congenital EV infections.

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