CLINICAL AUDIT SUMMARY

1.0 Name of audit

Diagnosis and Recognition of Congenital Cytomegalovirus in Northern Ireland

2.0 Personnel involved

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Regional Virology Laboratory, RBHSC, Paediatric Pathology, BHSCT.

3.0 Date of audit

September 2011

4.0 Type of clinical audit (e.g. national, individual discipline etc)

A review of the diagnosis of congenital cytomegalovirus (CMV) infection over a 10 year period from 2001-2011 within Northern Ireland

5.0 Background to audit

CMV is a herpes virus of the betaherpesvirinae associated with mild or asymptomatic primary and secondary infections, establishing latency after initial infection. Thus most individuals are unaware they have been infected by CMV (Cannon and Davis 70). The frequency of reactivation increases with loss of immune competence.

In-utero congenital CMV infection can result in a wide range of symptoms including: hepatomegaly, splenomegaly, thrombocytopenia, petechiae, chorioretinitis, jaundice, seizures, microcephaly, intra-cranial calcification, intrauterine growth retardation(Gaytant et al. 245-56; Revello and Gerna 680-715; Townsend, Peckham, and Tookey). Sensorineural deafness can develop as a late sequela of congenital infection and later development of permanent childhood hearing impairment (PCHI). Children with mild and profound PCHI have evidence of congenital CMV in 8% and 23% of cases respectively (Korver et al. S27-S31).

Testing for congenital infection with CMV is usually indicated by the presence of IUGR or the presence of symptoms of congenital infection at birth. A prior diagnosis of maternal CMV infection during the pregnancy is also an indication for testing the newborn while detection of asymptomatic infection would require a screening program for newborns to be in place. Early diagnosis and treatment of symptomatic congenital infection is associated with
a reduction in the severity of long term sequelae. Benefits from treating asymptomatic infection are not yet established.

In the United Kingdom the seroprevalence of CMV in childbearing age women is approximately 50% (Townsend, Peckham, and Tookey), the prevalence of congenital infection is about 3/1000 births and around 10-15% of congenitally infected infants are symptomatic at birth (Dollard, Grosse, and Ross 355-63). In a separate study, confirmation of congenital CMV in the UK and Ireland was found by detection of CMV in urine by PCR in 76/86 (88%) infected children and of these 78/86 (91%) were confirmed at <7 days of age (Townsend, Peckham, and Tookey). The quoted prevalence of congenital infection is likely to be an underestimate because CMV infection is not routinely sought in cases of stillbirth or intra-uterine death (Townsend, Peckham, and Tookey). The prevalence of neurological and sensory sequelae are being increasingly recognized (Dollard, Grosse, and Ross 355-63), although symptoms of congenital infection may not be recognized for several years, making establishing a diagnosis in older children problematic (Picone et al. 34-38).

Diagnosing Congenital CMV Infection

In order to distinguish between congenital and postnatal CMV infection, CMV must be detected in the urine, blood or tissue of individuals within the first 2 – 3 weeks of life (Grosse et al. S32-S36) and this benchmark was used to confirm congenital infection in this audit. Testing after this period will identify both congenital and perinatally acquired infection, the latter being of little clinical significance while the former is associated with significant short and long term morbidity. Serum CMV IgG and IgM were assayed using Abbott Axysm and Architect Elisa immunoassays. CMV DNA was detected by nested PCR until 30/4/2007 and by a quantitative TaqMan from that date. Detection of (a) serum CMV IgM or (b) CMV DNA in urine, blood, cerebrospinal fluid (csf) or respiratory secretions in the first 3 weeks of life confirmed congenital infection; detection of viral DNA in CSF is associated with an increased likelihood of neurological involvement and is a marker for initiating treatment. Testing of stored Guthrie bloods for CMV DNA was also used to establish congenital infection retrospectively in one patient.

6.0 Objectives of audit

The objectives of the audit were to determine the number of tests undertaken for congenital CMV infections at birth, in relation to the numbers expected using current clinically accepted good-practice standards of evidence, and to determine how many were confirmed.
Screening for immune susceptibility during pregnancy is not advised by the UK National Screening Committee and there are no explicit standards for the routine investigation of newborn children for congenital infection. However, there are clinical indications where congenital infection should be considered and that have been used in this audit to establish standards against which to measure current performance. The following parameters have been used to guide when appropriate to investigate for in-utero congenital CMV.

(a) Maternal CMV infection has been suspected or confirmed during pregnancy.
(b) The pregnancy experienced problems during gestation or at delivery where CMV in-utero infection should be excluded.
(c) The obstetric team referred the placenta for pathological investigation.
(d) The pregnancy ended prematurely.
(e) The pregnancy ended in miscarriage – (<22 weeks).
(f) The pregnancy ended in late fetal loss (22-24 weeks) or stillbirth (>24 weeks).
(g) The newborn presented with symptoms in keeping with in-utero infection.

8.0 Data collection

Requests for maternal infection during pregnancy and for evidence of congenital infection at birth were retrieved from Regional Virology records. The annual number of placental tests, late fetal loss and stillbirths were obtained from paediatric pathology. The number of miscarriages were obtained from DHSSPS - Strategy for Bereavement Care. 2:25. 1-6-2009. The estimate of the number of late fetal losses and stillbirths undergoing autopsy came from the CEMACH report - Perinatal Mortality Report 2007; 1-74. 2009.

Routine laboratory data was extracted using the relational database Paradox version 4.5 (Boreland) and analysed using the statistical software package Epi-Info (CDC, Atlanta, GA). Results for children up to 5 years of age from 01/01/2001 to 05/09/2011 were reviewed. These included all tests for CMV DNA in urine, blood, respiratory secretions, CSF and autopsy specimens, the latter were referred from paediatric pathology. Serum results for CMV IgG and IgM for the same age group were also reviewed. Patients were analysed in 2 categories: (1) ≤ 21 days of age; (2) >21 days to 5 years of age.
9.0 Results

Potential Annual Number of Requests for Congenital CMV Infection

Approximately 150 pregnant women and 100 newborn infants are tested each year for evidence of CMV infection. Annually approximately 10% of all pregnancies could have a placenta referred for a range of conditions including growth restriction, fetal distress and infection; premature labour could also be an indication for placental referral. Thus up to 2500 pregnancies could have placentas tested for conditions affecting pregnancy. The annual number of miscarriages, late fetal losses and stillbirths is approximately 2500, 30 and 90 respectively. Approximately half of the late fetal losses and stillbirths undergo autopsy (CEMACH, 2009). While clearly there are many other causes for the conditions mentioned, potentially over a 12 month period with 25000 live births, up to 5000 requests for congenital CMV could be expected.

Confirmed Congenital Infection – Diagnosed ≤ 21 days

From January 2001 to August 2011 a total of 1180 patients ≤ 22 days old and with a male:female ratio of 1.2:1 were tested for congenital CMV infection. Out of these, 13 patients were confirmed to have had an in-utero CMV infection, including one through retrieval and testing of a Guthrie Dried Blood Spot. There was a female bias in those with confirmed infection, with 11 female and 2 male infections confirmed. Of the 12 surviving neonates with confirmed infection, 7 had repeat samples submitted for follow-up analysis.

This cohort expressed a range of classical features of congenital CMV infection including: 5 IUGR; 8 petechiae, including thrombocytopenia; 2 Jaundice; 1 Hepatomegaly; 2 Splenomegaly; 1 Microcephaly; 1 per rectal bleed; 1 retinal haemorrhage; 1 sensorineural hearing loss. Two children were asymptomatic and were tested because of confirmed maternal infection during pregnancy and there was one stillbirth at 35 weeks gestation.

Possible Congenital Infection – Diagnosed > 21 days

Over the same period 2713 patients >21 days and <5 years old and with a male:female ratio of 1.4:1 were tested for CMV infection. Of these, 19 had confirmed CMV infection, all in the first year of life. There was a male bias with 6 female and 13 male infections. There was 1 case of Sudden Unexplained Death in Infancy Syndrome. Fourteen neonates had repeat samples submitted for follow-up analysis.

While some of the clinical features would be in keeping with congenital CMV infection, others appeared incidental to a diagnosis of CMV. The clinical spectrum included: 1 spasm; 4 pyrexia; 2 irritable; 1 developmental delay; 1 failure to thrive; 1 metabolic disorder; 1 microcephaly, 1 cerebral palsy, 1
premature delivery, 1 hepatomegaly, 1 nephritis, 1 cot death, 1 petechiae, 1 IUGR.

10.0 Length of audit

Audit undertaken during September 2011.

Outcomes/recommendations/actions taken

This audit estimated that up to 5000 pregnancies per annum could be considered for exclusion of congenital CMV. However the actual number, as indicated by tests undertaken in the first 3 weeks of life, was approximately 120, 2.4% of the potential number. This suggests a lack of awareness and lack of knowledge concerning congenital CMV infections.

Actions

Discuss audit findings with appropriate parties in particular paediatric and obstetric practice.

Consider undertaking a GAIN regional audit to gauge awareness of congenital CMV amongst health care professionals.

Place Audit on appropriate website to facilitate access.

12.0 Proposed re-audit

The nature of this audit, spanning a 10 year period, would be difficult to repeat in the immediate future. However it clearly highlights the need for a better appreciation of when congenital CMV should be considered in routine clinical practice, in particular because of a more pro-active approach to initiating early treatment in symptomatic infants. A specific regional audit to that end should be considered through the GAIN network.

Reference List


