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Basic Medical Surveillance Essentials for children with Down syndrome

DSMIG BEST PRACTICE GUIDANCE -NEONATAL

Down syndrome accounts for 1:1000 live births in the UK. This figure has been relatively stable since 1989.[1]

Neonates with Down syndrome are at an increased chance of a wide range of medical problems in the neonatal period. Based on current evidence the following good practice recommendations have been made to help guide clinical practice.

Recommendations (seeing accompanying pathway)

1. Antenatal

Some babies with Down syndrome are diagnosed antenatally and the responsibility for counselling lies with the local antenatal team. Booklets on screening tests in pregnancy are produced by Public Health England, NHS Scotland and Down syndrome Ireland [2] [3] [4]The Down's Syndrome Associations (England & Wales, Scotland and Ireland) also provide booklets on continuing the pregnancy.[5] [6] [7]

Royal College of Midwifes Accredited Training entitled "Tell it Right, Start it Right" is provided by the Down's Syndrome Association to help professionals deliver easily understood, accurate, balanced and up to date information about Down syndrome[8].

A system for liaison with the local CDC team/lead professional should be established in case prospective parents require further information at any time antenatally.

2. Diagnosis

Postnatal Diagnosis If the diagnosis has not been made antenatally and there is clinical suspicion of Down syndrome, a health professional with sufficient knowledge of Down syndrome to answer immediate questions, should discuss this ideally with both parents and support.[9] Blood should be sent for genetic analysis to confirm the diagnosis. Blood should also be taken at the same time for FBC and blood film, see section 9. Haematology.

For babies diagnosed in the antenatal period: repeat genetic testing is recommended if the diagnosis was made by CVS, early amniocentesis (18-22 weeks) or cfDNA. Repeat testing may not be recommended if the diagnosis was made by a late amniocentesis (third trimester). The QF-PCR testing used antenatally has a low false negative rate (0.3%) but backup karyotyping may be required. Please check with your local genetics laboratory as they may have a specific policy.[10 11 12]

A meeting should be arranged with the parents to share the full confirmatory karyotype results and answer any further queries.

When there is confirmation of Down syndrome an information pack should be given. This may include:

- The Down syndrome PCHR insert[13]
- Information on the relevant Down's Syndrome Association and their New Parent Guide[14 15 16 17 18 19]
- Any information about local support groups
- Down's Syndrome Heart Group[20] where relevant

The parents and baby should be introduced, or referred, to an appropriate local lead professional for Down syndrome as soon as possible to ensure appropriate multidisciplinary input. This may become more complex if the baby has significant health problems that require intervention in the newborn period and that may involve transfer to other hospitals e.g. paediatric cardiology, paediatric surgical centres etc.

The obstetrician, midwife, GP and HV should also be informed as soon as possible.

3. Growth and feeding

38 weeks is the most common gestational age at birth for babies with Down syndrome with their average birth weight being 2979g [21]. There is currently no available growth data for babies born before 37 completed weeks with Down syndrome. Standard charts for prematurity should therefore be used up until term and then growth plotted on the Down Syndrome Growth Charts subsequently.[22] Ensure that the PCHR Down syndrome growth chart insert is also used.

Help and support should be given for mothers who wish to breastfeed as well as supporting those who want to bottle feed. Specific supporting

literature for parents is available from the Down's Syndrome Associations[23] [24] [25] and La Leche League International[26] . It may be useful to involve a speech and language therapist with a special interest in feeding. A naso-gastric tube may be needed to supplement feeds, whilst breast feeding is being established.

For babies with Down syndrome early weight loss may be more than 10% and it often takes longer than 2 weeks to regain birth weight[27]. Early weight loss greater than 10%, which is not quickly recovered, or undue delay in regaining birth weight (>4 weeks) indicates a need for careful clinical evaluation for feeding difficulties or major underlying pathology. By 4 weeks, if there is no serious medical problem, most will be on a centile close to their birth centile.

4. Heart

Between 40 and 60% of babies with Down syndrome have congenital heart defects. Of these 30 - 40% are complete atrioventricular septal defects (AVSD)[28] [29] [30] Most AVSD can be successfully treated if the diagnosis is made early and the baby referred for full corrective surgery before irreversible pulmonary vascular disease (PVD) is established[31] [32] [33] [34] [35] Other lesions can usually be approached with less surgical urgency. With the increasing availability of cardiac ECHO it is recommended that all newborn babies with a confirmed diagnosis of Down syndrome have an ECHO as a first line investigation. When this is not available a careful clinical examination and ECG should be carried out. On the basis of this the degree of urgency for echocardiogram and expert cardiac assessment can be established as follows[36].

Symptomatic babies referred for urgent cardiac assessment.

• Those with abnormal clinical signs or ECG abnormality (in particular a superior QRS axis[37]) are potentially at high risk for PVD (pulmonary vascular disease) and it is desirable that they are referred and seen within 2 weeks of birth for expert clinical assessment and echocardiogram by someone with appropriate paediatric cardiology training.

• Those with no abnormal clinical signs or ECG abnormality on initial examination may nevertheless have cardiac disease. These babies should all be referred and seen within 6 weeks of birth by someone with appropriate paediatric cardiology training for further clinical assessment and echocardiogram

Babies diagnosed later in the neonatal period

These should have immediate ECG and clinical examination and accelerated referral to someone with appropriate paediatric cardiology training with the aim, wherever possible, of achieving the 6 week deadline given above.

Babies with a prenatal diagnosis of Down syndrome

In the absence of evidence about the sensitivity of fetal echocardiography we suggest that those who had a fetal echocardiogram should still follow the above neonatal pathway.

The Down's Heart Group provides parent support for any child with a heart problem

5. Thyroid function

The incidence of congenital hypothyroidism in Down syndrome is more common and occurs in 1-3.6% of children [38 39 40]. The newborn screening programme for congenital hypothyroidism based on TSH analysis should detect most children with congenital hypothyroidism [41]. No separate routine neonatal testing of thyroid function is required or recommended for the following reasons unless there is clinical suspicion.

Thyroid-stimulating hormone (TSH) surges soon after birth, resulting in thyroxine (T4) concentrations that are higher in the first postnatal week than at any other time of life and in circulating triiodothyronine (T3) concentrations that are three to four times higher than in the fetus. Neonatal screening takes into account these natural changes but standard laboratory testing does not. The only time that standard laboratory TFTs should be done in the neonatal period is when there is clinical suspicion of thyroid disease that has arisen.

Ensure that the Guthrie TSH is returned as negative. If the result is abnormal there is a standard procedure in place which your local reference laboratory will institute. This usually entails taking a TFT blood sample and commencing thyroxine immediately. Refer on immediately to your local paediatric endocrinologist if you need support and advice for this.

Be aware that transient neonatal hyperthyrotropinaemia (raised TSH but normal T4) may also occur[42]. If detected this should be discussed with your local paediatric endocrinologist.

6. Hearing

All newborn babies with Down syndrome should have the Universal Newborn Hearing Screen.

Otitis media with effusion (OME or glue ear) affects up to 35% of children with Down syndrome at birth[43] [44] [45]. There is a higher incidence of ossicular abnormalities in Down syndrome which may present with a conductive hearing loss[46]. The incidence of sensorineural hearing loss identified at newborn hearing screening in children with Down syndrome is higher than in the general population at 4-6% [45] [47]. Extremely narrow ear canals can interfere with testing and hearing abilities.

Passing the UNHS does not preclude the need for ongoing surveillance[48]. If they fail their UNHS it should be checked that the screener has referred immediately for further investigation.

7. Vision

Compared to the general population there is a tenfold increase in congenital cataract[49] and infantile glaucoma may also occur[50]. Nystagmus is present in at least 10%[51]. As with all children, a trained person should examine newborns with Down syndrome for congenital cataract and other eye anomalies and this should be repeated at the 6 week check[52]. Refer any possible abnormalities immediately to an ophthalmologist.

8. Gastrointestinal Tract

As with all newborn babies the expectation is that they should pass meconium within 24-48 hours and any bilious vomiting is abnormal. Very careful routine examination of the external anal area should occur.

Around 7% of children with Down syndrome have congenital malformations of their gastrointestinal tract. Defects included oesophageal atresia/tracheoesophageal fistula (0.4%), pyloric stenosis (0.3%), duodenal stenosis/atresia (3.9%) and anal stenosis/atresia (1.0%).[53]

Also more common is Hirschprung's disease (HD) (incidence 2.6% in Down syndrome). Recto-sigmoid HD is the commonest type but long-segment HD is significantly more frequent in HD with coexisting Down syndrome. The coexistence of HD and Down syndrome is also associated with higher rates of pre-/postoperative enterocolitis, poorer functional outcomes and increased mortality. [54]

9. Haematology

The blood cell morphology and blood counts in neonates with Down syndrome differ from those in babies without Down syndrome in several ways.[55 56 57] On average, the haemoglobin and haematocrit are higher in babies with Down syndrome and ~20% are polycythaemic (haematocrit >0.65). If a diagnosis of Down syndrome is made antenatally, the practise of delayed clamping of the cord should be avoided, to prevent pathological polycyaethemia. The platelet count is also lower in babies with Down syndrome than those without Down syndrome: in 50% the platelet count still remains above the normal range (>150 x 10^9/L) but the remaining babies have either mild/moderate (platelets 50-140 x 10^9/L; 40%) or, in 10% of cases severe thrombocytopenia (platelets <50x10^9/L)[55]. Common causes of neonatal thrombocytopenia (such as sepsis or intrauterine growth restriction) occur as often or even more frequently, in neonates with Down syndrome and therefore it is important to recognise that thrombocytopenia should not be attributed to the diagnosis of Down syndrome without consideration of other

Transient Leukaemia of Down Syndrome (TL-DS) is a congenital leukaemia unique to neonates with Down syndrome or mosaic trisomy 21. It is also sometimes called Transient Abnormal Myelopoiesis (TAM) or Transient Myeloproliferative Disorder (TMD). It is driven by mutations in the haematopoietic transcription factor gene *GATA1* and is only seen in conjunction with trisomy 21[58 59 6061]. It occurs in 5-30% of neonates with Down syndrome. It is a clonal disorder characterized by circulating megakaryoblasts and dysplastic changes in the peripheral blood film with variable degree of multisystem organ involvement[55 62 63]. TL-DS can be present without any signs or symptoms and is only identified through examination of the blood film and/or *GATA1* mutation analysis as no haematological features are specific for TL-DS[55]. TL-DS may be associated with hepatosplenomegaly, pericardial/pleural effusion/ascites or rash, however no clinical features are specific for TL-DS. The majority of cases of TL-DS (~80%) resolve spontaneously by 3

months of age. Severe cases however can develop liver fibrosis, cardiopulmonary and renal disease resulting in death in up to 15-23% of cases[64] [65] [66]. Treatment for severe TL-DS is usually given at the physician's discretion with considerable variation in treatment policies between different centres. This variation may lead to early fatality. The UK guideline on investigation and management of TL-DS is now in place that recommends low dose cytarabine for 5-7 days for the treatment of TL-DSwith good effect [65] [66] [67].

Approximately 20-23% of those with resolved TL-DS will go on to develop myeloid leukaemia of Down syndrome (ML-DS) in the first 4 years of life[65]. All cases of TL-DS and ML-DS have the same *GATA1* mutation. Treatment outcomes in ML-DS are better as compared to non-DS acute myeloid leukaemia (AML) partly due to increased sensitivity to chemotherapy but also due to lower risk of disease relapse with a 90% cure rate if treated early [68] [69] [70].

All neonates with Down syndrome should therefore have a FBC and blood film taken in the first 2-3 days of life at the same time as their genetic tests with particular attention to the peripheral blood blast percentage assessed by a haematologist with experience at reviewing neonatal blood films. Any neonate with a blast percentage of >10% and/or clinical features suggestive of TL-DS should be discussed urgently with the regional paediatric haematology centre and a peripheral blood sample should be sent for *GATA1* mutation analysis in an accredited laboratory. Any child who did not have a peripheral blood blast cell percentage performed in the first 3 days of life or in whom there was significant intra-uterine growth retardation (when blast counts may be supressed) should be considered to be still at risk of clinical problems of TL-DS in the first 4-8 weeks of life and should be monitored accordingly. GATA1 mutation analysis should be considered.[71]

If TL-DS is associated with clinical symptoms, the neonate should be monitored closely until there is spontaneous resolution of symptoms and thereafter with a FBC and blood film 3 monthly until the age of 2 years and then 6 monthly until the age of 4 years. Abnormal blood counts or blood film appearance should prompt early investigation. If TL-DS is diagnosed and the neonate is asymptomatic then a FBC and blood film should be monitored 3 monthly until the age of 2 years and if there are no then 6 monthly until 4 years of age.

10. Renal

Several congenital anomalies of the renal and urinary tract have been reported in children with Down syndrome, the most common of these being renal hypoplasia, obstructive uropathy including posterior urethral valves, glomerular microcysts, hypospadius and undescended testicles.[72] Some abnormalities may be picked up on antenatal scans and should be dealt with as appropriate.

There is no evidence at present to recommend routine postnatal screening for renal tract abnormalities. Check that the antenatal scans of the renal tract were reported as normal and that the baby passes urine normally. If in any doubt request a renal tract scan.

A careful examination of genital area should be performed. In boys, it should be recorded that both testis are descended, as undescended testis is associated with a higher incidence of testicular cancers. If the testis are undescended a referral should be initiated to the urological surgeons before 6 months of age.

11. Hips

There is no evidence of increased risk of developmental dysplasia of the hips in Down syndrome at birth[73]. There is therefore no current recommendation to routinely screen the hips with ultrasound if a baby is born with Down syndrome. Routine neonatal examination of the hips is recommended with ultrasound being if there is additional breech presentation, family history of DDH or abnormal hip examination.

The pathogenesis and clinical course of hip dysplasia in Down syndrome is different than idiopathic developmental dysplasia of the hip. Hip instability develops after birth secondary to musculoskeletal disorders associated with Down syndrome[74]. Clinical monitoring of hip stability should therefore continue regularly after the newborn period.

12. Miscellaneous

All routine immunisations are advised.

RSV immunisation is not specifically recommended unless there are additional relevant cardiac and prematurity factors.

A marbled skin appearance (cutis marmorata) or bluish discolouration of the hands and feet (acrocyanosis) is very common and often persists beyond the neonatal period is of no consequence

Summarised Pathway

Indications of Down syndrome at birth:

1. Senior Paediatrician and Midwife to discuss with both parents
2. Inform Local Paediatrician responsible for following up children with Down syndrome
3. Take blood for:
    a. FBC and blood film
    b. Confirmatory genetic testing. Initial QR-PCR testing results may be available in 3 days whereas karyotype results take 7-10 days.

Diagnosis Confirmed:

1. Give a new parent information pack, including the Down Syndrome 2011 PCHR insert
2. Inform Obstetrician, Midwife, Paediatrician responsible for following up children with Down syndrome , Health Visitor and GP

Additional notes for performing the Newborn Check:

1. Plot growth on 2011 Down syndrome growth chart (A4 or PCHR insert). If born prematurely use standard premature growth charts.
2. Symptomatic babies require immediate cardiac referral. If the baby is asymptomatic but there are abnormalities on cardiac examination refer to a paediatrician with appropriate cardiac training to be seen within 2 weeks. Even if cardiac examination and ECG are normal arrange for a cardiac ECHO to be done within 6 weeks.
3. TSH is done by heel prick newborn blood spot screening. Ensure the result is received and acted upon.
4. Ensure neonatal hearing screen is completed and audiology follow-up is arranged for 8 months, even if screening is normal.
5. Refer on to Ophthalmology only if there are any abnormalities, such as suspicion of cataracts.
6. Ensure bowels opened within 24 hours and feeding is established. Encourage and support breast feeding.
7. Treat polycythaemia and thrombocytopenia if indicated. If there is an abnormal blood film, discuss with a paediatric haematologist as regards further investigation (e.g. GATA1 gene, repeat film) and treatment.
8. Check that urine has been passed and the antenatal renal scan was normal. Arrange a repeat renal ultrasound if in any doubt.

9. Refer on for hip ultrasound only if there is any clinical instability, a history of breech delivery or a family history of Developmental Dysplasia of the Hip.
10. Ensure that the parents are aware of the follow up plan and the expected service provision in your local area, including the contact details of your local support group for parents with children with Down syndrome.

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Steering group for DSMIG Best Practice Guidance - Neonates
Dr Rebecca Ferris Consultant Paediatrician, Hampshire Hospitals Foundation Trust
Dr Chris Hardie Lead Paediatrician, Solent Community Paediatrics
Dr Claire Mccall Associate Specialist Community Paediatrics, Nottingham
Dr Carl Harvey Consultant Paediatrician, City Hospital Sunderland
Dr Abi Sharpe ST7 Paediatrics Wessex Rotation

Thanks also for their contribution to:
Dr Neha Bhatnagar Consultant Paediatric Haematologist, Oxford (Haematology section)
Dr Nik Johnson Consultant Paediatrician, Huntingdon
Dr Bob Ironton Consultant Neonatologist, University Hospital Southampton
Members of parents support group Andover Twenty1

Enquiries to: Down's Syndrome Medical Information Services c/o Staff Library, Duncan Macmillan House, Porchester Road, Nottingham NG3 6AA. UK Tel 0115 9691300 ex 13268 Email:info@dsmig.org.uk

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