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Early Diagnosis of Congenital Heart Disease in the Neonatal Period

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1. Introduction

Congenital heart disease (CHD) is present in 40-60% of children with Down syndrome (DS) and it is the principal variable that determines the morbimortality during the first two years of life of these patients. Advances in fetal echocardiography are providing highly accurate diagnoses of congenital heart disease prior to delivery, making it possible to plan the delivery-room management of these newborns. However, the majority of neonates who have congenital heart disease will not require delivery room resuscitation in excess of routine care. Although cardiovascular evaluation is a standard component of the diagnostic work-up in patients with Down syndrome, physical examination alone does not predict the presence or absence of congenital heart disease in the neonatal period. The changeover of fetal to neonatal circulation with the decrease in pulmonary vascular resistance (increase in pulmonary blood flow), the increase in systemic vascular resistance (the lower-resistance placenta is excluded from the circulation) and the timing of functional closure of the ductus arteriosus may determine the clinical presentation.

As physical examination alone is not sufficient to identify cardiovascular anomalies in neonates with Down syndrome and the early detection can improve the outcome of congenital heart defects, we need a newborn screening strategy, because failure to recognise these defects early in life can have serious consequences. Echocardiographic examination provides extensive anatomic and hemodynamic information noninvasively, in real time, and at relatively low cost. A routine echocardiography should be performed in this population in the neonatal period.

The aims of this chapter are:
3. Correlation between cardiac physical examination and echocardiography.

2. Congenital heart disease in Down syndrome

The association between DS and CHD has been well established since 1950, when the incidence and type of CHD present in newborns and infants with SD was thoroughly described (Evans, 1950)
In general population, CHD is one of the most common serious congenital anomalies, with an incidence about 1% occurring in up to 2% of liveborn children, and in an even higher percentage of fetuses. Children with DS have an increased incidence of CHD, 40%-60% is the range described in the world literature. The life expectancy of children with DS depends primarily on the risk of mortality in the first year of life and CHD is the major cause of mortality during the postneonatal period with 70% of cases (Weijerman et al, 2008).

Nevertheless, there are several factors that influence to determine the true incidence on CHD. Many forms of CHD are now detected by fetal echocardiography with early prenatal diagnosis of chromosomal abnormalities, and the parents may choose to abort these fetuses. Fetal echocardiography has shown that certain ventricular septal defects, may be detected in utero but have disappeared at the time of birth or within 6-12 months after. Studies using neonatal echocardiography have shown prevalence of muscular ventricular defect as high as 53 per 1000 live births, most babies were asymptomatic and most defects were small with early spontaneous closure rate of 89% within 1 to 10 months. These muscular ventricular defects may result from delayed physiologic development rather than from disease (Roguin et al, 1995). If they are not all included, this leads to the underestimation of the true incidence.

In general population, ventricular septal defects are the most common form of CHD, accounting for approximately 30%, but in DS patients, the endocardial cushion defect, also known as atrioventricular septal defects (AVSD), is the leading type, up to 40%(fig.1), followed in frequency by ventricular septal defect (fig.2), atrial septal defect, patent ductus arteriosus and tetralogy of Fallot. Recent reports have shown that the distribution of congenital heart disease in children with DS may vary with ethnicity (De Rubens et al, 2003). Atrioventricular septal defects show the most significant sex and ethnic differences with twice as many affected females, and compared with whites, twice as many blacks, and half as many Hispanics (Freeman et al, 2008).

![Fig. 1. Echocardiographic s apical four-chamber image demonstrating a complete atrioventricular septal defect (laminar flow without aliasing).](https://www.intechopen.com)

AVSD is caused by abnormal embryologic development of endocardial cushions and the bulboventricular fold. AVSD can be complete (common atrioventricular canal), partial...
AVSD can be complete (common atrioventricular canal), partial (atrial septal defect of the ostium primum type or cleft anterior mitral leaflet) or intermediate form, it can be isolated or combined with other cardiac anomalies, such as tetralogy of Fallot. Conversely, approximately 80% of all AVSD occur in children with DS.

Left-side obstructive defects such as coarctation of aorta and valvar aortic stenosis are rare, and transposition of the great arteries has not been reported in Down syndrome.

Many chromosomal syndromes are associated with a variety of CHD. Several of these syndromes show a fixed pattern of CHD, such as 22q11-deletion syndrome, Noonan syndrome, Turner syndrome and Williams syndrome. Down syndrome also shows a fixed pattern of CHD, with overrepresentation of septal defects and underepresentation of left-side obstructive defects and transposition of the great vessels. This observation, indicates
that a locus on chromosome 21 is involved in the development of CHD. Although no single gene candidate has yet been identified to be responsible for this phenotype, genes for several matrix-related proteins (alfa-1 and alfa-2 type VI collagen, Down’s Syndrome Cell Adhesion Molecule, integrin beta-2 and alfa-1 XVIII collagen) are located on chromosome 21. Overexpression of type VI collagen has been suggested to play a role in the pathogenesis of atrioventricular septal defects in DS (Vis et al, 2009).


The pulmonary circulation undergoes a near-instantaneous change from its high resistance state in utero to a low resistance circuit after delivery to allow adequate pulmonary perfusion. Delivery of the fetus from the uterus disrupts the umbilical-placental circulation and the functions of oxygen uptake and carbon dioxide removal are transferred to the lungs. The foramen ovale (fig.3) and the ductus arteriosus (fig.4) have to be closed functionally or anatomically to establish the adult circulation. Physical expansion of the lung, ventilation with oxygen and umbilical cord occlusion produce an increased in pulmonary blood flow and decrease in pulmonary vascular resistance. The pulmonary endothelium plays a crucial role in this adaption, the onset of breathing is associated with an increase in specific mediators such us nitric oxide and prostaclin (pulmonary vasodilators and inhibitors of smooth muscle cell proliferation), and a decrease of vasoconstrictors (angiotensin and endothelin-1).

Fig. 3. Echocardiographic subcostal four-chamber image demonstrating a patent foramen ovale.

If pulmonary vascular resistance does not fall normally after birth, pulmonary arterial pressure will not drop to normal postnatal level, and pulmonary blood flow adequate for oxygen needs may not be established. This phenomenon has been named persistent pulmonary hypertension of the newborn (PPHN), and may result from several condition (perinatal asphyxia, meconium aspiration) (Suesaowalak et al, 2010). A wide variety of cardiac disorders has been reported to cause PPHN and have been grouped into five types based on the physiology of the lesion (Long, 1990):
Group 1. Obstructions to pulmonary venous drainage (obstructed total anomalous pulmonary venous drainage, cor triatriatum, mitral stenosis...)

Group 2. Congenital cardiomyopathies (endocardial fibroelastosis, myocarditis...).

Group 3. Obstructions to left ventricular outflow (aortic atresia, critical aortic stenosis, interrupted aortic arch, coarctation...).

Group 4. Obligatory left-to-right shunts (cerebral arteriovenous malformations, hepatic arteriovenous malformations, complete atroventricular septal defect...)

Group 5. Miscellaneous cardiac disorders (Ebstein anomaly, tricuspid atresia, pulmonary atresia, transposition of the great vessels...)

Children with Down syndrome have an increased risk for developing pulmonary hypertension. The cause of pulmonary hypertension in this population is multifactorial and may be due to both anatomical and physiological alterations in the pulmonary circulation, including the presence of congenital heart disease with persistent left-to-right shunts, chronic upper airway obstruction, or abnormal pulmonary vasculature growth. Although damage to the pulmonary vasculature occurs over time, there also appears to be a subset of Down syndrome patients who develop pulmonary hypertension in the neonatal period. Neonatal DS patients have a greater incidence of persistent pulmonary hypertension of the newborn (PPHN) compared to the general population, and suggests that there may be something intrinsically related to DS that put these patients at increased risk for PPHN (Cua et al, 2007).

Fig. 4. Echocardiographic parasternal short-axis image demonstrating a patent ductus arteriosus (red flow at the ductus arteriosus and blue flow at both pulmonary arteries).

4. Correlation between cardiac physical examination and echocardiography

4.1 Clinical examination

Although CHD is present at birth, there are often no signs and most babies are asymptomatic. Skilled physical examination, a sensitive and specific screening tool in older children, does not always distinguish between neonates with or without CHD (Griebsch, 2007).

Wren et al. (1999) found no clinical signs in the first weeks in some children with DS, with major cardiac malformations and associated pulmonary hypertension, even in some who progressed to irreversible pulmonary vascular disease.
A normal neonatal examination in children with DS does not therefore exclude a serious CHD. Basic neonatal characteristics, Apgar scores, birth weight and gestational age are not different in children with DS with and without CHD (Weijerman et al, 2010). The natural history of specific heart defects depends on the transitional circulation in the neonatal period, so the timing of the routine examination is very important. Heart murmurs have a prevalence of between 0.6% and 4.2% in newborns and are mistakenly considered a hallmark of heart disease (Patton, 2006). Transient murmurs due to tricuspid regurgitation (fig.5) and physiological peripheral pulmonic stenosis (fig.6) are the most common innocent murmurs in neonates (Du et al, 1997).

Fig. 5. Echocardiographic apical four-chamber image demonstrating a tricuspid regurgitation (blue jet from right ventricle to right atrium).

Practising pediatricians currently have limited experience in discriminating innocent from pathological murmurs. Detection of a murmur depends on the examiner’s skill and experience, the timing and the frequency of examination, and the conditions under which examination takes place. Detection of a murmur on routine examination may be a clue to the presence of heart disease and offers the possibility of early, presymptomatic diagnosis. Early referral of all asymptomatic babies with murmurs is recommended for early definitive diagnosis by echocardiography. However, the absence of a murmur does not exclude the presence of potentially serious heart disease (Ainsworth et al, 1999). Murmurs of atrioventricular septal defect and septal defect, the most common forms of CHD in SD, emerge after the decline in pulmonary resistance and may happen after neonatal discharge.

4.2 Electrocardiography
Electrocardiography (ECG) do not improve the sensitivity of the clinical assessment in the detection of CHD. Atrioventricular septal defects is associated with abnormal ECG (superior QRS axis), but most of the CHD have normal results on ECG (Mackie et al, 2009).
Sensitivity and specificity of a superior QRS axis to diagnose complete atrioventricular septal defect is 100% and 96.8%, respectively. However, the predictive value of neonatal ECG for other CHD is poor (Dennis et al, 2010).

4.3 Chest radiography
There is no evidence that chest x-ray (CXR) is a useful addition for neonatal diagnosis of CHD. CXR alone missed 39% of the cases of complete atrioventricular septal defect, whereas ECG missed only 17%. Combining CXR, ECG and clinical examination gave little added benefit only 15% missed (Dennis et al, 2010).

In the evolution, but out of neonatal period, radiographic manifestations in infants with left-to-right shunts include cardiomegaly, prominence of the pulmonary vasculature, and dilatation of the central pulmonary arteries. With the severe and longstanding process, pulmonary artery hypertension appears, this shunt flow decreases and reverse, resulting in peripheral pruning of pulmonary vessels. As the pulmonary vascular resistance increases, if the congenital CHD is not corrected, the heart size may decrease (Suesaowalak et al, 2010).

4.4 Pulse oximetry
Cyanosis in the newborn is difficult to detect at clinically important levels, murmurs may be missed or over diagnosed and femoral pulses are challenging to assess. Together with early discharge and failure to assess infants identified as at risk. The introduction of additional oximetry screening could achieve better results at the relatively small cost. Pulse oximetry is a simple, non-invasive method of monitoring the percent saturation of haemoglobin which is saturated with oxygen. The pulse oximeter consists of a probe attached to the infant’s finger, toe or edge of the foot, which is in turn linked to a computerised display of the percentage of haemoglobin saturated with oxygen and the heart rate. The examination can be performed by a junior doctor, midwife or other health professional. The equipment required is portable and can be used in the home and hospital. An oximeter identifies hypoxemia and is dependent on a good peripheral circulation and so does not work reliably when a baby has
a low blood pressure or is dehydrated, for example. Pulse oximetry may identify babies with cyanotic CHD but not defects that only associated with murmurs or delay or absent pulses. Nevertheless, some authors think that pulse oximetry is a promising alternative newborn screening strategy (Knowles, 2005; Meberg, 2009), but others not (Reich, 2008; Sendelbach, 2008). Pulse oximetry cannot detect all cases of CHD, and parents should be informed, and hence, a negative test result does not exclude the possibility of heart disease. According to the American Heart Association and American Academy of Pediatrics, the usefulness of oximetry in clinical studies is not well established (Class IIb, Level of Evidence C), and future studies are needed to determine whether this practise should become standard of care in the routine assessment of the neonate (Mahle et al, 2009). Therefore, the screening with pulse oximetry should be carried out together with a clinical examination, never alone.

4.5 Echocardiography

Echocardiographic examination provides extensive anatomic and hemodynamic information noninvasively, in real time, and at relatively low cost. Echocardiographic windows are better in the newborn than at any other age because the lungs (impenetrable to ultrasound) do not get in the way as much, and the heart and great vessels are nearer the probe. The echocardiography must be a systematic study with the standard views (left parasternal, apical, subcostal and suprasternal) and completed with Doppler ultrasound (colour Doppler, pulsed Doppler and continuous wave Doppler). Echocardiography is useful for initial evaluation, cardiac defects, level of shunting, degree and directions of shunts, severity of pulmonary arterial hypertension, follow-up of the treatment and ventricular function can be delineated systematically. A routine echocardiography should be performed in this population in the neonatal period (AAP’s Committee on Genetics, 2001). A patient is considered to have an abnormal cardiac physical examination if there is a cardiac murmur and/or cyanosis or an abnormal systemic arterial oxygen saturation, but a newborn without congenital heart disease but with persistent pulmonary hypertension of the newborn (PPHN) may present a cardiac murmur due to transient tricuspid insufficiency of cardiac dysfunction, and cyanosis due to right-to-left shunting of blood across the patent ductus arteriosus and the foramen ovale. These clinical manifestations may alert the neonatologist and suspect the presence of a congenital heart disease, but in deed, there is not.

The diagnosis can be confirmed by echocardiography with color Doppler imaging and documenting right-to-left shunting of blood through fetal circulatory pathways (ductus arteriosus and foramen ovale), in the absence of CHD (fig 7, Fig 8). Contrast echocardiography is performed by rapidly injecting approximately 1ml of saline/blood mixture into a peripheral vein while capturing a four-chamber view of the heart. The simultaneous appearance of bright echoes from cavitations in the fluid in the right ventricle and left atrium documents right-to-left atrial shunting. Because the right-to-left atrial shunt may be predominately of inferior vena cava, as it is in the normal fetal state, injection of fluid into a vein draining to the inferior vena cava may yield the best results (Fineman, Heymann & Morin, 2001).

Doppler echocardiography allows estimation of pulmonary artery systolic pressure. Because pulmonary artery and right ventricle systolic pressure are nearly equal in the absence of
steno\(s\)is of right ventricle outflow tract, pulmonary artery systolic pressure is commonly estimated by techniques that measures right ventricle systolic pressure. In the method most commonly used, the tricuspid regurgitation jet is used to calculate the right ventricular-right atrial pressure gradient (Snider & Serwer, 1990). Transthoracic echocardiography is useful for evaluation of severity of pulmonary arterial hypertension and ventricular function can be delineated systematically. The abnormal motion of the interventricular septum and the eccentricity index estimate right ventricular pressure overload. The Tei index and the tricuspid annular plane systolic excursion (TAPSE) correlate with right ventricular function (Suesaowalak et al, 2010).

**Fig. 7.** Echocardiographic parasternal short-axis image demonstrating a patent ductus arteriosus with right-to-left shunt (blue flow).

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5. Potential benefits of early diagnosis.

Because of the high incidence of a significant CHD in children with DS, the early recognition of CHD can lead to the optimal management of the defect and emphasizes the importance of an early echocardiography of neonates with DS.
Early diagnosis of CHD in DS is important firstly because both the parents and the paediatrician need to know the implications of the heart defect. Secondly some major malformations with pulmonary hypertension may show no signs and may progress to irreversible pulmonary vascular disease before the heart defect has been recognised. When fetal echocardiography was introduced into clinical practise, it become possible to study the spectrum of lesions associated with DS in prenatal life (fig.9) and the early diagnosis is of paramount importance (Paladini et al, 2000).

Fig. 9. Fetal echocardiography demonstrating a complete atrioventricular septal defect.

5.1 Pulmonary arterial hypertension
About half of all babies with DS will have CHD, and in around one-third of these this will comprise a complete atrioventricular septal defect with high risk of pulmonary vascular disease due to high pulmonary blood flow. Among the numerous causes of pulmonary arterial hypertension, left-to-right shunt and chronic upper airway obstruction are frequently encountered in children with DS. Obstructive sleep apnoea is common in children with SD, affecting 30-50% of this patient group compared with 3% of the general paediatric population. This may result from a number of factors, including hypotonic upper airway, adeno-tonsillar hypertrophy, macroglossia, glossoptosis, flattened mid-face and narrow nasopharynx in these patients (Hawkins et al, 2011). This association of CHD in DS with pulmonary arterial hypertension, has led a neonatal screening and, as medical treatment becomes increasingly unsuccessful, early definitive cardiac surgery is usually undertaken at 3-6 months of age (Vohra et al, 2010). Many reports have demonstrated safe and effective repair in infants with atrioventricular septal defects within the first few months of live, and the presence of DS is not a risk factor (Lange et al, 2007).
In the past, infants with complete AVSD were initially palliated with pulmonary artery banding to prevent pulmonary vascular disease, followed by complete repair at a later stage to reduce mortality and morbidity. Better perioperative care and improvements in surgical
and cardiopulmonary bypass techniques, allowed surgeons to successfully perform early repair. Nevertheless, there are situations in which early primary repair is not feasible or is accompanied by unacceptable risk. Reasons include unfavourable intracardiac anatomy (unbalanced ventricular morphology, associated lesions, or both), associated non cardiac malformation (exomphalos), or poor clinical condition (infection, chronic lung disease, renal or liver dysfunction, gastrointestinal or neurological complications). In these situations palliation with pulmonary artery banding followed by late repair is recognized as a viable surgical option (Dhannapuneni et al, 2011).

5.2 Nutrition
Failure to thrive is common in children with congenital heart disease. Infants with CHD are particularly at risk of energy imbalance that can involve deficiencies of specific nutrients, or insufficient total caloric intake. Malnutrition undermines the outcome of corrective surgical operations and postoperative recovery. Most infants with CHD have a normal weight for gestational age at birth but develop nutritional and growth problems in early infancy. Weight tends to be more effected than height; even so, almost half of infants younger than 2 years are stunted (Nydegger and Bines, 2006).

Mechanisms linking CHD to malnutrition may be related either to decreased energy intake and/or to increased energy requirements. Decreased energy intake are in relation with anorexia and early satiety of these patients, decreased gastric volume caused by hepatomegaly, malabsorption due to edema and chronic hypoxia of the gut, pharmacologic agents, fluid restriction...

Increased in energy requirements can be due to increased respiratory rate accompanying congestive heart failure, cardiac hypertrophy, recurrent infections, increased activity of sympathetic nervous system, increased basal temperature...

The development of malnutrition depends on the type and severity of the cardiac lesion and associated disease condition. Infants with cyanotic heart lesions (tetralogy of Fallot) frequently have decreased weight and height compared with healthy infants. Chronic hypoxia is an important factor in anorexia and inefficient processing of nutrients at the cellular level. Atrioventricular septal defect and septal defect, the most common forms of CHD in DS, are acyanotic heart lesions but if there is a large left-to-right shunt, have reduced weight gain but growth may be maintained during infancy. However, in the presence of elevated pulmonary pressure, severe growth failure frequently develops (Varan et al, 1999).

Associated genetic condition, Down syndrome, is another crucial factor and also influence energy intake, gastrointestinal absorption, expenditure, and growth expectations (Nydegger and Bines, 2006).

Most treatment strategies aim to facilitate "catch-up" growth, providing extra calories and protein that exceed the Recommended Dietary Allowance for age. However, there is no generally accepted set of guidelines that define appropriate caloric intake for catch-up growth. Early diagnosis of CHD in DS, brings out the nutrition challenge, the most effective nutrition strategies for children with CHD (Forchielli et al, 1994). Nutritional support via percutaneous endoscopic gastrostomy allows the safe delivery of the caloric intake needed in children with CHD and significant feeding-related difficulties (Ciotti et al, 2002).

5.3 Prevention of infective endocarditis
It is recommended that parents and carers of all children with CHD should be given information about infective endocarditis preventive measures. Infective endocarditis is an
uncommon but life-threatening infection. Despite advances in diagnosis, antimicrobial therapy, surgical techniques, and management of complications, patients with infective endocarditis still have high morbidity and mortality rates related to this condition. The development of infective endocarditis is the net result of the complex interaction between the bloodstream pathogen with matrix molecules and platelets at sites of endocardial cell damage.

The American Heart Association (AHA) guidelines for infective endocarditis prophylaxis were published in 1997. The 1997 document stratified cardiac conditions into high-, moderate- and low-risk (negligible risk) categories, with prophylaxis not recommended for the low-risk group. Nevertheless, since this document, many medical societies and physicians have questioned the efficacy of the prophylaxis. The quality of evidence was limited to a few case-control studies or was based on expert opinion, clinical experience, and descriptive studies that utilized surrogate measures of risk. “The Committee” of AHA extensively reviewed data and published the updated recommendations in October 2007. This new document is intended to identify which, if any, patients and procedures may possibly benefit from infective endocarditis prophylaxis, and result in greater clarity for patients, healthcare providers, and consulting professionals (Wilson et al, 2007).

5.4 Prevention of Respiratory Syncytial Virus infection

Children with DS have an increased incidence of respiratory tract infections which might be associated with CHD, abnormal airway anatomy and physiology, hypotonia, and aspiration. However, children with DS and without CHD, also have a high incidence of respiratory morbidity and might be explained by an aberrant immune system as well (Bloemers et al, 2010).

Respiratory syncytial virus (RSV) is an enveloped, nonsegmented, negative-strand RNA virus of the family Paramyxoviridae that causes respiratory tract infections in children. In the Northern Hemisphere, the peak infection season is November through April. By two years of age, most children will have had an RSV infection. Bronchiolitis, a lower respiratory tract infection, is often caused by RSV. An RSV infection is diagnosed based on patient history and physical examination. RSV is recognized as the leading cause of hospitalization among young children worldwide. Infants of young chronologic age and children with predisposing factors, such as premature birth, pulmonary disease, or hemodynamically significant congenital heart disease, are most susceptible to serious illness. Children with DS have an increased risk of being hospitalized for RSV-induced lower respiratory tract infection, indicating DS as a risk factor (Bloemers et al, 2010). Unlike other viruses, immunity to RSV infection is incomplete and short lived, and reinfection is common throughout life. RSV infection remains difficult to treat, and prevention is a worldwide goal. Initial infection with RSV affords limited protection to reinfection, yet repeated episodes decrease the risk for lower respiratory tract illness. The development of palivizumab, a monoclonal antibody that can bind to a specific antigenic site on the virus and prevent cell-to-cell spread of infection has since become the mainstay of RSV illness prevention in preterm infants and those with significant congenital heart disease. Palivizumab, the only monoclonal antibody approved for the prevention of RSV lower respiratory tract disease must be administered monthly throughout the RSV season and does not always prevent serious RSV illness. Palivizumab is administered intramuscularly at a dose of 15 mg/kg.
once every 30 days, for a maximum of 5 doses. The American Academy of Pediatrics (AAP) published a policy statement on the use of palivizumab in November 1998, revised it in December 2003, and the last statement in the 2009 Red Book recommendations, safety and efficacy have been established for infants born at or before 35 weeks’ gestation with or without chronic lung disease of prematurity and for infants and children with hemodynamically significant heart disease (AAP, Committee on Infectious Diseases, 2009).

6. Conclusion

There is an increased incidence of congenital heart disease (CHD) and persistent pulmonary hypertension in Down syndrome (DS) neonates. A normal neonatal examination in children with DS does not therefore exclude a serious CHD. Clinical examination alone is insufficient to detect CHD in newborns. Failure to recognise these defects early in life can have serious consequences. The child’s future health, and indeed survival, may be severely compromised by late diagnosis. Neonatal echocardiography is the most effective single procedure and must be carried out by an appropriately trained person. A routine echocardiography should be performed in this population in the neonatal period.

7. References


This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book focuses on exciting areas of research on prenatal diagnosis - Down syndrome screening after assisted reproduction techniques, noninvasive techniques, genetic counselling and ethical issues. Whilst aimed primarily at research worker on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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