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Anaesthesia for the Dysmorphic Child

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INTRODUCTION

As anaesthetists, we frequently encounter the dysmorphic child, sometimes unkindly referred to as the "FLK" (Funny Looking Kid). If we have due warning and ample time at our disposal (and perhaps limitless money) we can thoroughly investigate all of these children preoperatively. This is not, however always feasible or possible. Investigations need to be directed. Sometimes these children present in the emergency situation and there is not sufficient time to investigate them fully. In particular, they are encountered in Plastics & Craniofacial, Orthopaedics and less commonly in ENT & Neurosurgery. My aim today is not to do an exhaustive list of all the syndromes that we may encounter, but rather to go through a practical way in which to approach these children.

STRUCTURE

Definitions
Aetiology
Embryology
Clinical Approach
Why is the dysmorphic child important to the anaesthetist?

- Associated abnormalities
- Malignant hyperthermia
- The difficult airway
- Difficult vascular access
- Psychological issues

Conclusion

DEFINITIONS

Malformations:
This refers to abnormalities in structural development. They tend to occur from the 3rd to 8th weeks of gestation. They may constitute absence of, or alteration in, a structure.

Disruptions:
These are insults to structures after they have developed, ultimately resulting in destruction. Examples include bowel atresias (due to vascular accidents) and amniotic bands.

Deformations:
This refers to abnormalities due to mechanical force – club feet can occur in this manner. Most, however, resolve with time e.g. pressure effects occurring in twins.

Dysplasias
These are abnormalities affecting a particular tissue type. They usually have a genetic cause which ultimately results in abnormal intermediary metabolism. They tend to take some time to present. An example is achondroplasia.

Syndromes:
This refers to a group of anomalies linked together due to their common aetiology. Strictly speaking, a syndrome implies that a diagnosis is known e.g. Downs Syndrome (Trisomy 21)

Association:
This is the presence of 2 or more abnormalities in the same child for which the aetiology is unknown. Examples include:
CHARGE – Colobomas, Heart defects, Atresia of choanae, Retarded growth, Genital Abnormalities & Ear abnormalities.
VACTERL – Vertebral, Anal, Cardiac, TracheoEsophageal; Renal & Limb.

Complex:
This is a mix of abnormalities which are linked due to their close location on the body (e.g. some of the craniofacial abnormalities).

Sequence:
This is a series of ordered consequence due to a single cause. In simple terms; A causes B, B causes C, C causes D. If C is not present, D will not occur. Examples include DiGeorge, Pierre Robin and Poland sequence. In Pierre Robin, the initial insult is failure of the mandible to develop normally. As a secondary effect, a cleft palate and posterior displacement of the tongue occurs.

AETIOLOGY [4]

A) Genetic Disorders
1) Chromosomal Disorders

- Too many e.g. Trisomies
- Too few e.g. Monosomies
- Deletions
- Additions
- Inversions
- Ring Formation
- Mozaicism

2) Single Gene disorders
- i.e. Autosomal Dominant, Sex Linked Recessive

3) Multifactorial

B) Non- Genetic Disorders
I.e. Teratogens, which refers to any external factor that damages the developing foetus.

Table 1: Common Teratogens[4]

TERATOGEN	EXAMPLE	RESULT
Metabolic	Diabetes Mellitus	Spine, legs, heart, kidney, genitals
		Sacral agenesis
		Femoral hypoplasia (Unusual Facies Syndrome)
	Hypothyroidism	Goitre, growth retardation, intellectual
	Hyperthermia	Poor growth, midfacial hypoplasia, cleft lip & palate, CNS abnormalities
Epilepsy		Drug induced Hypoxaemia related
Infections	Syphilis	Jaundice, hepatomegaly, skin lesions, osteitis, rhinitis, nephrosis, hydrocephalus / microcephalus
	Rubella	Microcephaly, microphthalmia, cataracts, deafness, PDA, intellectual disability
	Toxoplasmosis	Hydrocephalus, microphthalmia, calcification of parasites, intellectual disability
	Cytomegalovirus	IUGR, microcephaly, chorioretinitis, deafness, hepatomegaly, periventricular brain calcification, intellectual disability
	Herpes Simplex Virus	Microcephaly, ocular abnormalities, PDA, intellectual
	Varicella	IUGR, scarred skin, Limb reductions, chorioretinitis, intellectual disability
External Agents	Alcohol Cocaine	Foetal Alcohol Syndrome Bowel, Renal, Genital, Limb
	Herbal Thalidomide Chemotherapy Anticonvulsants Anticoagulants Hormones Isotretinoin Antibiotics	Phocomelia Masculinisation Face, heart, CNS, thymus, IUGR Tetracyclines – teeth; Aminoglycosides – Renal, deafness
	Radiation	

EMBRYOLOGY

The possibility of teratogenic insult can occur throughout a pregnancy, but it begins in the 3rd week of development. This period, known as gastrulation, is the time where the embryo develops all three germ layers – ectoderm, mesoderm & endoderm. At this point, the embryo is very vulnerable to insult. The problem of caudal dysgenesis occurs when there is insufficient development of mesoderm with resultant absence / abnormality of the lower limbs, urogenital system & lumbosacral vertebrae. Resultant clinical problems include lower limb hypoplasia / fusion, renal agenesis, imperforate anus & genital abnormalities – constituting a portion of the well known VACTERL.

Most organ development occurs between the 3rd and the 8th weeks after fertilization. This period is known as the period of organogenesis. Stem cell populations form at this point and go on to produce organ systems. Exposure to teratogens at this point therefore produces gross abnormalities. Interestingly, as organogenesis occurs in a highly regimented manner, if an abnormality occurs, one can pinpoint the time of the insult to within a few days (e.g. an anencephalic child would have been exposed between days 23 – 25).

A reminder of the origins of organ systems follows:

Ectoderm — CNS; Peripheral NS; Sensory epithelium of eyes, nose & ear; skin, hair & nails
Glands – pituitary, mammary, sweat
Teeth enamel

Mesoderm — Myotomes (muscle)
Sclerotomes (cartilage & bone)
Dermatomes (subcutaneous tissue)
Vasculature – including the heart
Urogenital (NOT bladder)
Spleen
Adrenal cortex

Endoderm — Epithelium of GIT, respiratory tract, bladder
Thyroid, parathyroid
Liver, pancreas
Tympanic cavity & auditory tube (epithelium)

Why is this important? A congenital abnormality in one of the above could very likely be associated with a deficit in another organ of the same

embryological origin. Abnormalities involving the placenta or its membranes, however, are not associated with organ system abnormalities. Amniotic bands, for example, are associated with amputations or rings which most commonly affect the limbs but may also affect craniofacial structures. Abnormalities of internal organs are not related.

CLINICAL APPROACH

It seems that the golden rule is: If you find one abnormality, actively search for another one! This is because of the nature of our embryological development. Sometimes, when presented with a child, a diagnosis is unclear and the surgeons label the child as 'syndromic' or as having 'some dysmorphic features'. In this case, at the preoperative visit, one should specifically look for associated abnormalities. This is particularly important as sometimes the anaesthetist is the first to notice dysmorphic features in a child. So, what constitutes normal?

Height

Tall or short?

Standardised growth charts are available for determining expected height for age and sex. A small child may have an underlying chronic disease, particularly cardiac, renal or respiratory. Short stature is also a feature of some specific conditions e.g.. Achondroplasia. An excessively tall child is also a sign of a possible problem, e.g. Marfan's syndrome.

Weight

Underweight

As with short stature, underweight is associated with chronic underlying conditions. It is, however, a feature of more specific problems, such as Turner's syndrome.

Overweight

Better known, are the anomalies associated with large birth weight (e.g. Beckwith Wiedemann) or obesity that develops later in childhood e.g.. Prader-Willi; Bardet-Biedl.

Developmental Delay

This is a very non-specific feature but a sure sign that there is an underlying problem and that the child warrants closer assessment.

Other CNS

Hypotonia occurs with myopathies and dystrophies. This may be associated with motor developmental delay.

Head size

As with paediatric height and weight, standardised charts are available for Occipital Head Circumference – the child may have macrocephaly or microcephaly. These may occur on their own, but are often part of a greater problem. Microcephaly is part of Foetal Alcohol Syndrome & Angelman Syndrome, for example. Macrocephaly is common, for example in Mucopolysaccharidoses.

Head shape

E.g. Craniosynostosis or stenosis – wide variety of different head shapes depending on which suture lines are involved. Beware the airway difficulty in a child with an abnormally shaped head!

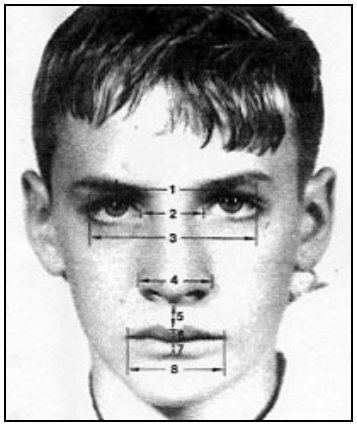
Fontanelles

Delayed closure. The posterior fontanelle usually closes at 3 months of age. The anterior fontanelle closes at 9 – 18 months[6]. Additional fontanelles may also be present e.g. 3rd fontanelle in Trisomy 21 although this may be a normal variant.

Facial Symmetry

Some cases of facial asymmetry are obvious e.g. Goldenhar Syndrome. Others are more subtle, such as Facial hypoplasia / dysplasia.

Figure 1: Common Facial Measurements [7]



(1) Interpupillary distance, (2) inner canthal distance, (3) outer canthal distance, (4) interalar distance, (5) philtral length, (6) upper lip thickness, (7) lower lip thickness, and (8) intercommisural distance.

Eyes
As shown above, charts are available that give normal values for eye measurements. These include the outer canthal, inner canthal and interpupillary measurements. By plotting a child on these charts, Hypotelorism or Hypertelorism can be diagnosed. Other abnormalities include epicanthic folds, abnormal palpebral fissures, colobomata, cataracts, ptosis, blue sclera, prominent eyes or even absent eyes.

Ears
Abnormalities include misshapen, tags or low set ears. If the top of the ear falls below the line drawn between the 2 inner canthi & around the head, the ears are low set. Importantly, ear abnormalities are linked with airway & renal abnormalities due to their shared time of development. Beware pre-auricular skin tags as these have been linked with a difficult intubation[8].

Nose
A multitude of abnormalities can affect the nose – it may be abnormally large or small in relation to the rest of the face, or the nares may by hypoplastic. Choanal atresia is relatively frequently encountered. It is associated with multiple abnormalities, for example CHARGE, Pfeiffers' Treacher Collins, Trisomy 18 etc.

Mouth
Abnormalities include macro or microstomia and trismus. Not only are these clues to coexisting abnormalities, they may make intubation difficult. Cleft lip & palate is commonly an isolated problem, but it is also associated with at least sixty-six[3] congenital syndromes / sequences. Therefore, always actively search for associated anomalies in these children.

Tongue
Macro or microglossia are common. Besides potentially causing a difficult intubation, tongue abnormalities are a sign of other problems. Microglossia occurs in Freeman Sheldon and Moebius sequence; Macroglossia in Hunters, Hurlers & Beckwith-Wiedemann. Cleft or duplicated tongues can occur, with obvious difficulties for the anaesthetist.

Teeth
Abnormalities can vary between anodontia (complete absence) to hypodontia to abnormal shape, size, placement and loss.

Jaw
Micrognathia and prognathism are also associated with other abnormalities as well as being problematic in their own right due to intubation challenges.

Neck
The neck may be short or webbed, giving clues to a possible diagnosis. Multiple bony abnormalities can occur, from atlanto-axial subluxation in Trisomy 21, to fusion in Klippel Feil.

Hands
A variety of abnormalities are recognised: Polydactyly (may be isolated); syndactyly; short fingers or abnormally long thin fingers (arachnodactyly).

Feet
Rockerbottom feet occur in Edwards Syndrome (Trisomy 18)
Club feet – like cleft lips & palates, these may be isolated or they may be a feature of a more complex problem. In this case too, actively search for co-existing abnormalities. If in any doubt, the child warrants further investigation

Skeletal
These abnormalities include short, long, or asymmetrical limbs. Absence of long bones can occur (e.g. radial aplasia in VACTREL). Spinal and sternal abnormalities must be excluded.

Genitals
Abnormalities may be isolated or part of another syndrome.

Skin
Depigmentation, lesions, café au lait spots etc.

Surgical Problems:
Most neonatal emergencies can occur as part of a syndrome / malformation. E.g: Abdominal wall defects, Pyloric Stenosis; Intestinal malrotation; Duodenal Atresia; Tracheo-oesophageal fistula; Congenital diaphragmatic hernia. Other paediatric surgical problems such as Abdominal or inguinal hernias, Hirschsprung disease and Nephroblastomas can also form part of a syndrome. Further investigation is based on clinical grounds as these problems may be isolated findings.

By using this method, a diagnosis can become clearer. For example a child identified to have short limbs and polydactyly may have either Chondroectodermal Dysplasia or Grebe Syndrome. This is especially important in the child who presents for surgery & who has a constellation of signs, but for whom a diagnosis has never been made. It must, however, be stressed that examination of the parents is very important. Sometimes, a child has atypical features, but these have been inherited from a parent

and are merely a normal variant. Be aware, however, that the parent too may have the syndrome, so this approach is not always helpful.

WHY IS THE DYSMORPHIC CHILD IMPORTANT TO THE ANAESTHETIST?

1) Occult, serious abnormalities that have not been identified
2) The link with Malignant Hyperthermia
3) The difficult airway
4) Difficult vascular access
5) Psychological problems / mental retardation resulting in extreme anxiety or difficulty with induction

1) SYSTEM ABNORMALITIES

A wide range of co-morbidity is associated with congenital abnormalities[9]

Cardiac disease

Intraoperative cardiac instability is the most common finding in syndromic children[9]. Therefore, the significance of an undiagnosed cardiac problem is obvious. The spectrum of cardiac disease is very broad, from cardiomyopathies (e.g. Duchenne's) to valvular disease (e.g. Marfan's) to shunts (e.g. AVSD in Trisomy 21). Some conditions are at risk for hypertension (e.g. Ehlers Danlos or Prader Willi). Do not forget to search for arrhythmias and cardiac failure. The most common structural defects are ventricular septal defects, atrioventricular septal defects; hypoplastic left heart and double outlet right ventricle[9]. Patients may present for cardiac surgery or for an unrelated procedure. Undiagnosed cardiac disease needs to be excluded. This is especially important in a patient with a problem known to include cardiac disease e.g. Trisomy 21, VACTREL or those listed in table 3 below. All dysmorphic children warrant a thorough clinical examination and directed investigation based on clinical findings. For obvious reasons, not all can be referred for investigation.

The difficulty lies with who should NOT be investigated. From my reading, I can suggest the following:

Children who require pre-operative cardiac investigation:

1) History or clinical examination suggests cardiac disease (e.g. Poor exercise tolerance or feeding difficulty; frequent respiratory tract infections with no obvious cause; signs of valvular disease, cardiac failure, arrythmias etc).

2) Primary myopathies, as outlined in table 2 below
3) Children with a diagnosis where cardiac involvement occurs 'frequently' (as outlined in Table 3 below)

Table 2[10]: Cardiac abnormalities in primary myopathies [*]

Impaired impulse generation and conduction
Myocardial thickening (posterior wall and septum >11 mm)
Left ventricular hypertrabeculation (>3 coarse trabeculations apically to the papillary muscles)
Dilatation of the cardiac cavities (left atrium >40 mm, left ventricle >58 mm)
Secondary valve insufficiency
Intracardiac thrombus formation
Reduced coronary vasodilative reserve
Heart failure (clinical diagnosis)
Systolic dysfunction (fractional shortening <30%)
Diastolic dysfunction
a) Classic (E/A ratio <1)
b) Restrictive (short tall E wave)
c) Pseudonormalization (in case of concomitant systolic dysfunction)

[*]Primary myopathies refers to all dystrophies, mitochondrial disorders and storage diseases.

Table 3: Syndromes and Disorders where Cardiac Involvement Occurs Frequently[3]:

3C Syndrome (Craniofacial, Cerebellar, Cardiac)	(100%)
DiGeorge sequence	(100%)
Holt-Oram (Cardiac Limb Syndrome)	(100%)
Mulibrey Nanism Syndrome	(100%)
Toriello-carey Sydrome	(90%)
Deletion 22Q11.2 Syndrome	(85%)
Trisomy 13	(80%)
CHARGE	(75 – 80%)
Cardio-Facial-Cutaneous Syndrome	(77%)
Duplication 3q	(75%)
Allagile's	(67%)
Trisomy 9	(66%)
Athyrotic Hypothyroidism Sequence	(65%)
Duplication 15q	(65%)
Deletion 4q	(61%)
Chondroectodermal Dysplasia	(60%)
Deletion 11q	(60%)
Costello Syndrome	(52%)
Carpenter Syndrome	(50%)
Duplication 10q	(50%)
Kabuki	(50%)
Smith-Lemli-Opitz Syndrome	(50%)
Triploidy Syndrome	(>50%)
Trisomy 18	(>50%)
Mowat-Wilson Syndrome (incl Hirschsprungs)	(45%)
1P36 Deletion Syndrome	(43%)
Multiple Lentiines Syndrome	(40%)
Trisomy 21	(40%)
Catel Manzke Syndrome	(39%)
Distichiasis-Lymphedema Syndrome	(38%)
VATERR	(37%)
Cat Eye Syndrome	(>33%)
Rubinstein-Taybi Syndrome	(33%)
Deletion 5p	(30%)

Table 4: Other Disorders with Frequent Cardiac Involvement (Exact Incidence not stated)[3]:

45 X
Acrocallosal Syndrome
Asplenia Syndrome
Beals Syndrome
CHILD Syndrome
Deletion 13q
Foetal Alcohol Syndrome
Foetal Valproate Syndrome
Fryns Syndrome
Geleophysic Dysplasia
Leroy I-Cell Syndrome (Mucolipidosis II)
Marfan Syndrome
McKusick-Kaufman Syndrome
Mucolipidosis Syndromes
Mucopolysaccharidoses
Noonan's
Pallister Hall Syndrome
Peters'-Plus Syndrome
Polysplenia Syndrome
Progeria
Retinoic Acid Embryopathy
Short Rib-Polydactyly Syndrome
Simpson-Golabi-Behmel Syndrome
Smith-Magenis Syndrome
Stickler Syndrome
Ulnar Mammary Syndrome
Werner Syndrome
Williams Syndrome
XXXXX Syndrome
Zellweger (Cerebro-Hepato-Renal Syndrome)

Important: Many of the obviously "abnormal" looking children, particularly those with cranio-facial abnormalities e.g. Treacher Collins and Pfeiffer's have no association with cardiac disease at all. Other children, e.g. those with Mowat Wilson have a high incidence of cardiac disease. This is linked

with Hirschsrungs. How many of us request an echo on children with Hirschsprungs?

Any child whose history or clinical examination is suggestive of cardiac disease, should have the following investigations performed:

- Baseline oxygen saturation on room air
- Chest radiograph
- Electrocardiogram
- Cardiology assessment – this may include echocardiography or cardiac catheterisation, where indicated[11].

Antibiotic prophylaxis is required for certain procedures. The tables below are taken from the latest AHA guidelines for infective endocarditis prophylaxis.[12]

Table 5: Conditions where Antibiotic Prophylaxis is Required[12]

TABLE 3. Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis for Which Prophylaxis With Dental Procedures Is Recommended

Prosthetic cardiac valve

Previous IE

Congenital heart disease (CHD)*

- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

†Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

Table 6: Antibiotic Regimens[12]

TABLE 5. Regimens for a Dental Procedure

Situation	Agent	Regimen: Single Dose 30 to 60 min Before Procedure: Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin*†	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

IM indicates intramuscular; IV, intravenous.

*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

Renal Disease

Some conditions list renal dysfunction as a central feature in the diagnosis (e.g. Polycystic Kidney Disease or Aniridia-Wilms Tumour Association). Others have renal dysfunction as an associated feature which may be subclinical e.g. Bardet-Biedl syndrome. The need for renal investigation and appropriate selection of drugs in these cases is obvious.

Skeletal deformities

Skeletal abnormalities vary broadly. Certain children have contractures, making positioning difficult. Others, such as those with Osteogenesis Imperfecta are prone to injuries or fractures even with gentle handling. Kyphosis and scoliosis occur quite frequently with the associated respiratory complications. Pulmonary function tests may be indicated in these patients. This is particularly problematic in myopathies and dwarfism. If in doubt, do request radiological investigation of the cervical spine. Instability and fusion can occur, contributing to the difficult airway.

Respiratory problems

Respiratory disease may be secondary to skeletal deformities or myopathies. Other mechanisms include chronic gastro-oesophageal reflux with pulmonary aspiration or repeated pneumonias in the immunocompromised patient. Chest radiographs and pulmonary function tests may be required. In some patients, perioperative physiotherapy and bronchodilator use is required e.g. in cystic fibrosis.

Metabolic Abnormalities
This is most relevant for diseases where the primary defect is in a metabolic pathway, e.g. phenylketonuria or glycogen storage diseases. Liver function tests and urea and electrolytes are important pre-operative investigations in these children. Drugs with hepatic or renal metabolism should be avoided as appropriate. Other children may develop metabolic problems secondary to organ involvement by their disease e.g. hypocalcaemia in DiGeorge sequence or hypoglycaemia in Beckwith –Wiedemann syndrome or glycogen storage diseases.

Haemopoietic or Vascular
A wide variety of haematological abnormalities can occur, ranging from anaemia, thrombocytopaenia to leucopaenia. Some syndromes are associated with significant blood loss at surgery, e.g. Duchennes and Noonan's.

Neuromuscular System
Here, dysfunction occurs mainly in the myopathic group of patients. It is clinically significant due to the risk of sudden cardiac arrest as well as sensitivity or altered responses to neuromuscular blockers.

Central Nervous System Degeneration
Some rare conditions produce severe and progressive neurological deterioration. These children are prone to seizures and anticonvulsant therapy is mandatory.

When it comes to clinical examination, it cannot be stressed enough that these children warrant examination from head to toe. Take care not to become 'distracted' by obvious pathology and then forget to exclude other abnormalities!

2) MALIGNANT HYPERTHERMIA (MH)

As we know, MH is associated with genetic abnormalities resulting in dysfunction of calcium homoeostasis, usually via the Ryanodine receptor. The different subtypes are as follows:[13]

- MHS1 – Central Core Disease (via the ryanodine receptor due to a defect in chromosome 19q13)
- MHS2 – Sodium channel, 17q11.2-q24
- MHS3 – Calcium channel, 7q21-q22
- MHS4 – Chromosome 3q13.1
- MHS5 – Calcium Channel 1q32
- MHS6 – Chromosome 5p

The following syndromes are associated with true MH and a trigger free anaesthetic is mandatory.[14]

King Denborough Syndrome
These children have a characteristic facies with micrognathia, a high arched palate, strabismus and ptosis. It is because of these children, perhaps, that a link was initially made between MH and strabismus surgery.

Central Core Disease
This is also known as "Floppy Infant Syndrome". These children appear normal at birth except for hypotonia. With age, features develop which include contractures, upper limb dislocations, chest and spinal skeletal abnormalities. It is caused by a genetic mutation at 19q13.1, the same site as type 1 MH.

Evans Myopathy
Features of this condition include: Bilateral ptosis, muscle wasting of the adductors and glutei, hypertrophy of the sternocleidomastoid, leg muscles and lordosis of the lumbar spine[11].

The following conditions have been linked to MH in the past:

- Freeman Sheldon syndrome
- Noonan's (but perhaps because the King Denborough phenotype is so similar)
- Schwartz-Jampel Syndrome
- Larsen Syndrome
- Myopathies and dystrophies, amongst others.

Many of the isolated cases have not been proven as true MH. It is not the norm to perform a trigger free anaesthetic on these children, although close monitoring for MH is mandatory.

Recently, a distinction has been made between syndromes associated with true malignant hyperthermia and "MH like" reactions. Other syndromes, particularly the Muscular Dystrophies, tend to present with similar clinical features to MH, but with a different pathophysiology.

3 forms of MH Like syndromes exist:[15]. They have been documented only in patients with Duchenne's and Becker Muscular Dystrophy. They are related to volatile administration. Succinylcholine is contraindicated in these patients.

1 – Acute onset of hyperkalaemic arrest

This condition is characterised by massive hyperkalaemia (ranging between 6.9 – 12 mmol/l), occuring between induction and in the immediate postoperative period (i.e. in the recovery room). No patients received any succinylcholine – the condition is associated with volatile use alone. It has occurred with halothane, isoflurane and sevoflurane. Interestingly, patients show no signs of hypermetabolism prior to cardiac arrest. The mechanism of hyperkalaemia is massive rhabdomyolysis.

2 – Gradual Rise in Temperature and Heart Rate

A small number of patients have been documented who developed tachycardia and mild hyperthermia (maximum 38.2^0C) in association with halothane administration. These features resolve spontaneously after withdrawal of the halothane.

3 – Postoperative Rhabdomyolysis without Cardiac Arrest

These patients develop significant, delayed rhabdomyolysis after the administration of volatiles.

The malignant Hyperthermia Association of the United States (MHAUS) states:

"The pathophysiology of the (above three clinical conditions) is different to that of MH. Cardiac arrest related to MH is usually preceded by rapidly rising endtidal carbon dioxide, muscle rigidity, acidosis and hyperthermia, and most often occurs during anesthetic administration rather than in the postoperative period. In such cases, the cause… is significant metabolic and/or respiratory acidosis rather than hyperkalaemia."[16]

These "MH like" syndromes have been given the name AIR – Anaesthesia Induced Rhabdomyolysis. This distinction has been made due to the different clinical presentation and pathophysiology of AIR. Although disordered intracellular calcium is still central in the pathogenesis, it is the abnormal dystrophin which results in an unstable cell membrane, rather than an abnormal ryanodine receptor. You may feel that this discussion is, however, theoretical. Much like anaphylaxis and anaphylactoid reactions; MH and AIR present very similarly and are both precipitated by volatile anaesthetics. The difference lies in the management of these patients – although the standard supportive measures for MH apply to AIR, the use of dantrolene does not. Dantrolene is the mainstay of treatment of MH. Although its mechanism of action is not completely clear, it is postulated that it binds to the Ryanodine receptor isoform 1, thereby stabilising it and preventing further release of calcium from the sarcoplasmic reticulum[15]. As the pathophysiology of AIR involves a destabilised cell membrane with subsequent calcium leakage, there is no advantage in using Dantrolene. Indeed, in some of the patients documented with AIR, Dantrolene was used

but with no improvement in outcome[15]. The clue is said to be that severe rhabdomyolysis and hyperkalaemic cardiac arrest without preceding signs of hypermetabolism (hypercarbia, hyperthermia, tachycardia) suggests AIR, whereas progressive signs of hypermetabolisms culminating in rhabdomyolysis is more suggestive of MH. That being said, would any of you withhold Dantrolene in a hyperthermic child, with a muscle disorder, with a hyperkalaemic cardiac arrest?

The question remains – should dysmorphic children, or those in whom a muscular disorder is suspected (for example, those coming for muscle biopsy) be offered a trigger free anaesthetic? The evidence suggests that the answer is no. In a study by Flick et al[17], the records of 274 children (under the age of 21) who underwent muscle biopsy for a suspected neuromuscular disorder (myopathies, dystrophies, channelopathies) were assessed. Temperature, clinical records, postoperative CK and biopsy results were examined. Not one patient was found to have developed MH. The risk of MH in patients undergoing muscle biopsy was assessed to be <1.09%. A problem with this study is that it is retrospective in nature – only 274 patients were included as the remaining patients who underwent muscle biopsy over the allotted time period (77, total number 351) had a TIVA. Interestingly, a significant portion of these patients were strongly suspected of having Duchenne's (10 of the 77). Even though there is no clear evidence to support a trigger-free anaesthetic for a Duchenne's patient, traditional teaching has made a trigger free anaesthetic the norm, rather than the exception.

In conclusion, in my opinion, when faced with anaesthesia for a hypotonic child with a suspected neuromuscular disease, it is generally safest to perform the following assessment:

- A child suspected to have a muscular dystrophy – TIVA (definite risk of AIR and possible MH)
- A child suspected to have a mitochondrial myopathy – VIMA
  - The association between mitochondrial myopathies and MH has largely been dismissed
  - There is a risk of Propofol Infusion Syndrome, at a lower dose and after a shorter duration of treatment (i.e.the 4mg /kg/hr for >48hrs 'rule' does not apply in these children)[14].

If in doubt, a good history (including family history – only 10% of children with dystrophies do not have a family history[18]), physical examination and laboratory tests can help to differentiate the two – a raised CK occurs in Dystrophies and a raised serum lactate occurs with the Mitochondrial Myopathies. The safest approach is, if STILL in doubt, go for a TIVA.

3) THE DIFFICULT AIRWAY

In some cases, the child's airway is the predominant or only problem. Three common syndromes where the difficult airway almost always occurs are the following[19]:

1) Pierre Robin Sequence:

This consists of micrognathia, relative macroglossia with / without cleft lip or palate. The larynx is often more cephalad than usual. The combination of these factors can make direct laryngoscopy very difficult. The large tongue tends to cause upper airway obstruction, particularly if there is an associated cleft palate. Nursing the child prone can help to alleviate the obstruction, but tracheostomy may be necessary.

2) Treacher Collins Syndrome (mandibulofacial dysostosis):

These children tend to have a hypoplastic zygoma & mandible, macrostomia plus a cleft or high arched palate. In addition, abnormal dentition can occur.

3) Goldenhar Syndrome (Oculoauriculovertebral dysplasia):

This is characterised by micrognathia, cleft palate and unilateral mandibular hypoplasia. It may occur with the Klippel Feil anomaly where the neck is short and immobile.

In other cases, however, a less obvious difficult airway may be encountered. These children are the more concerning cases as more subtle signs are easier to miss. A history of persistant respiratory problems despite medical treatment may alert one to the possibility of malacias of the upper airway[11]. The difficult airway in a dysmorphic child can come about for a variety of reasons:

Neck:
A stiff or fused neck must be excluded pre-operatively. Children with CHARGE may have a short or webbed neck, for example.

Larynx:
May be hypoplastic, aplastic or stenotic (e.g. VATERR syndrome) MEN 2b or neurofibromatosis patients may develop neuromata of the larynx.

Epiglottis:
A cleft or bifid epiglottis can contribute to a difficult laryngoscopy.

Tongue:
Large or small tongues are a feature of many syndromes. Cleft tongues can also occur, as do oral webs.

Jaw:
Jaw abnormalities are usually obvious but actively search for them.

Mouth:
A small mouth can make insertion of a laryngoscope or supraglottic airway device difficult. Some conditions are associated with trismus.

Dentition:
A wide variety of abnormal dentition can occur, from aplasia (or anodontia) to hypodontia to irregular teeth to widely spaced teeth.

Nose:
If planning a nasal intubation, always be aware that hypoplasia of the nares or choanal atresia may prevent the passage of a nasal tube.

Figure 2:
ASA Difficult Airway Algorithm[20]

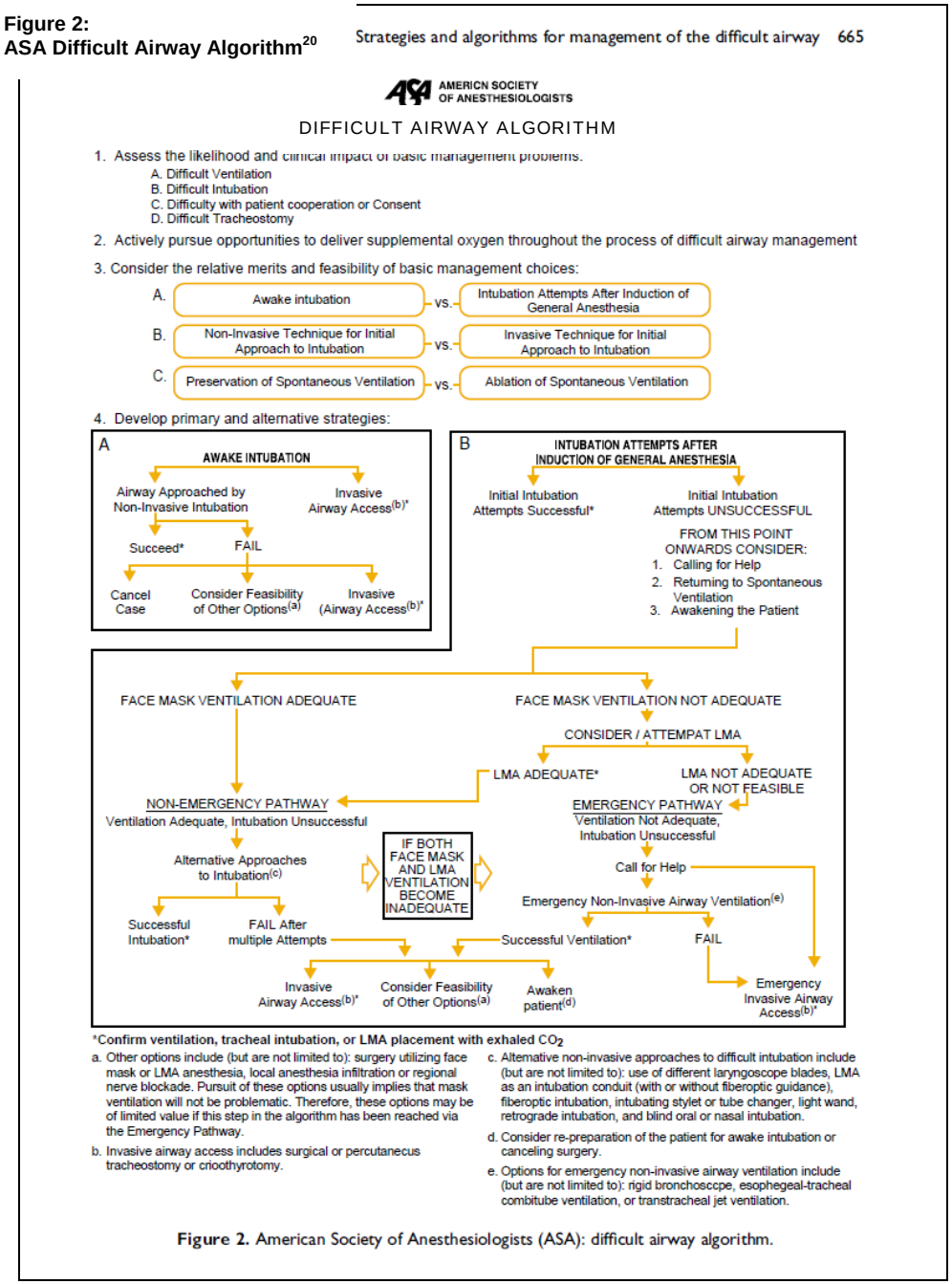


Figure 2. American Society of Anesthesiologists (ASA): difficult airway algorithm.

One should always be on the alert for a possible difficult intubation in a dysmorphic child, even if no 'red flags' have been detected pre-operatively. Most children will allow an airway examination, but there are obvious difficulties associated with a good airway examination in a neonate or infant. Hypotonic or myopathic children tend to have gastro-oesophageal reflux and pulmonary aspiration due to airway musculature weakness. Anti-reflux medications and strict adherence to NPO times are important in these children[11]. One should always be prepared for a possible difficult airway, and therefore, a difficult airway trolley should be immediately available for these cases. In general, a volatile induction allowing the child to breathe spontaneously is viewed as the safest option[11]. The introduction of paediatric sized laryngeal masks, particularly the paediatric Proseal™ has made the arena of the difficult airway a bit easier to manage.

What of the case of a possibly difficult intubation where volatiles are contra-indicated? The traditional approach to the paeds difficult airway is a volatile induction, with the child breathing spontaneously. If one is presented with a child with neuromuscular disease and a difficult airway, the challenge lies with keeping the child breathing spontaneously but still sedated enough in order to facilitate intubation, through whichever means is decided upon (e.g. fibreoptic bronchoscopy etc). A technique of Remifentanil plus Propofol infusion (mixture of 10mg/ml propofol plus 15-20 mcg/ml remifentanil) at a dose of 0.1ml/kg over 5 minutes has been described[21]. This technique was documented in fifteen paediatric patients. All (except one) breathed spontaneously and maintained their saturation > 95%. Personally, I would prefer to keep the drugs separate, so that either can be titrated individually as necessary. Dexmedetomidine is also an option in the child with a difficult airway[22]. A colleague in our department uses a mixture of ketamine and midazolam for children – ketamine 4mg/ml and midazolam 0.1mg/ml; infused at 1ml/kg/hour. This mixture ensures a co-operative comfortable child, but glycopyrrolate is necessary to prevent ketamine secretions.

4) DIFFICULT INTRAVENOUS ACCESS

Some conditions are associated with difficult intravenous access. An example is the Arthrogryposis group, such as Freeman Sheldon syndrome, due to limb deformities and thickened subcutaneous tissue[23]. The veins of children with Bardet Biedl are also notoriously difficult to cannulate due to increased subcutaneous tissue. This is important to know as help can be summoned early on and special care must be taken to prevent hypothermia during this period, particularly in an infant or neonate.

5) PATIENT ANXIETY / POOR CO-OPERATION

Many children become anxious in the unfamiliar environment of theatre. Mentally retarded children can, however, be even more challenging, particularly when they are older. A study from the 1990's showed that in 25% of paediatric patients, physical restraint was required to facilitate induction of anaesthesia[24]. This study used a general paediatric surgical population. The statistics for syndromic children, particularly those with mental retardation or behavioural disorders, would appear to be much higher. This problem is compounded by the fact that some children (particularly those with craniofacial abnormalities) have to have repeated surgeries and anaesthetics, and learn to fear the operating room. Talk to the parents of these children. They are often have good insight and can predict how their child will react.

A particularly challenging group of patients are those with cerebral palsy. In severe cases, there is a significant degree of mental retardation and so communication with the child can be difficult. Even children who are not mentally impaired may have attention deficit hyperactivity disorder or behavioural problems. Some syndromes are associated with autism, such as Prader Willi, Fragile X and Angelman's. Autistic children (or those with traits) can perform stereotyped behaviour & show hyperactivity. Any disturbance of their routine can lead to extreme anxiety and tantrums. These children can be very difficult to induce. The importance of good preparation and adequate premedication cannot be overemphasised. In the words of Jenny Thomas, when facing a hysterical child "Does one delay the operating list and attempt to give an oral premedication, or does one find the strongest adult in the theatre suite to restrain the child while either intravenous access is acquired, or 8% sevoflurane is administered via a facemask?... At what point does restraint become abuse?"[25]

Establishing rapport, judicious use of premedication and the presence of a parent can help to make the experience less traumatic for the child. In extremely anxious children, oral midazolam can be helpful. Due to its bitter taste, it should be mixed with a sweet flavoured syrup or juice. The dose is 0.5mg /kg. Sedative effects are seen within 5 – 10 minutes of administration, with peak effects within 30 minutes. This is not a drug to be given to the child in the ward, but rather in the holding area of theatre shortly before wheeling the child into the operating room. A review by Kox et al showed the midazolam premedication was effective in "reducing both separation and induction anxiety in children, with minimal effect on recovery times.[26]" Midazolam premedication is not, however, without complications (such as respiratory depression and disordered memory – children may remember patches of the induction experience, particularly traumatic

memories). It should, therefore, be reserved for only the extremely uncooperative child. The combination of ketamine plus midazolam can be used in the severely uncooperative child, either orally or intramuscularly (oral dose: Midazolam 0.25mg/kg plus ketamine 3mg /kg[27]).

Oral dexmedetomidine has also been used as a premedication in a small case series[28]. A dose of 1-4mcg/kg orally (of the standard intravenous preparation) was effective and palatable to the children. The majority of the children in this report were autistic or combative.

Note that children who are highly combative and difficult to induce, have a higher incidence of emergence agitation / delirium[29]. Therefore, it is best to avoid inhalationals with a rapid offset (Desflurane and sevoflurane) and to administer longer acting sedating drugs intraoperarively (e.g. Pethidine)

TAKE HOME MESSAGE

1) If you find one abnormality, look for another
2) If a child is booked electively, perform an internet search on the condition and alter your investigations and anaesthetic accordingly
3) Do not be overwhelmed by a glaringly obvious abnormality and then forget to look for other, equally important, ones
4) True MH is not that common
5) Always be prepared for the difficult airway

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APPENDIX

The following table summarises the major systemic associations with 36 of the more common disorders. It is by no means an exhaustive list (the original table contains 162 conditions). The reader is referred to this source for further reading.

Table 7: Key Features of Common Syndromes[9]

NAME	Description	A/irway	Resp	Reflux	CVS	CNS	Liver	Renal
Aarskog Syndrome:	Growth and mental deficiencies, dental anomalies, Cleft lip/palate, mild pectus, hypertelorism, shawl scrotum, brachydactyly cervical vertebral anomalies (including hypoplasia and synostosis), cardiac and renal defects	X	X		X			X
Achondroplasia	Short-limbed dwarfism, retardation of endochondrial bone formation, low nasal bridge, spinal canal stenosis, hyperextensibility Diminished lung vol, anterior epiglottis, difficult intubation, lumbar lordosis, Patent foramen ovale, narrowing spinal cord, small chest. Behavioural: Very high anxiety	X	X	X		X		
Angelman Syndrome:	"Puppet-like" gait, mental retardation, seizures, brachy-cephaly, inappropriate laughter. Hypotonia, EEG abnormalities, ataxia					X		
Apert Syndrome:	Irregular craniosynostosis, mid face hypoplasia, Narrow palate and airway, cleft palate; abnormal trach-eocartilage (48% of patients require trach-eostomy), hypertelorism and proptosis, syndactyly with "mitten" hand. heart and kidney defects, Agenesis of corpus callosum, ventri-culomegaly, increased intracranial pressure	X	X	X	X	X		X
Alagille Syndrome:	Growth retardation, typical facies, cleft palate, abnormal hepatic ducts, chronic cholestasis, hyper-cholesterolemia pulmonic stenosis. Butterfly and other vertebral anomalies,	X			X		X	X

NAME	Description	A/irway	Resp	Reflux	CVS	CNS	Liver	Renal
Beckwith-Wiedemann Syndrome:	Macroglossia, prognathism, macrosomia, organomegaly, omphalocele, neonatal hypoglycemia, ear creases, cardiac, liver and renal defects, hemihypertrophy, diaphragmatic eventration, immunodeficiency	X	X		X	X	X	X
Brachmann-de Lange Syndrome:	Growth and mental deficiencies, synophrys, thin downturning upper lip, hirsutism, micromelia, micrognathia, cleft palate, choanal atresia, cardiac and rib defects, malformed limbs, Diaphragmatic hernia. Hypertonia, seizures, apnea, aspiration	X	X	X	X	X		
CHARGE	Ocular *C*oloboma, *H*eart disease, choanal *A*tresia, *R*etarded growth and development and/or CNS anomalies, *G*enital anomalies, *E*ar anomalies and deafness. Also: vertebral anomalies tracheoesophageal Fistula, Renal defects, micrognathia, cleft lip / palate. Multiple cranial nerve abnormalities	X	X	X	X	X		X
Cri du chat Syndrome	Growth and mental deficiencies, microcephaly, epicanthal folds, asymmetric round face, cardiac and ear anomalies, cat-like cry. Cleft lip/palate, short neck, renal, cardiac and vertebral defects, scoliosis. Hypotonia, flaccid vocal cords	X	X		X	X		X
DiGeorge Sequence (Velo-Cardio-Facial Syndrome/22q deletion):	Hypoplasia to aplasia of thymus and parathyroids, cardiac defects, ear anomalies, immunodeficiency, hypocalcemia. Micrognathia, cleft palate, CNS and cardiac defects, scoliosis, laryngeal web. Seizures, hypotonia	X	X		X	X		

NAME	Description	A/irway	Resp	Reflux	CVS	CNS	Liver	Renal
Duchenne's Muscular Dystrophy:	Inability to walk,thoracolumbar scoliosis and cardiopulmonary impairment. Extensive blood loss, hypovolemic arrest, pneumothorax & cerebro-vascular accident; may have spinal fusion; MH	x	x			x		
Ehlers-Danlos Syndrome	Hyperextensibility of joints and skin and poor wound healing; Hypertensive responses to tracheal intubation and extubation. Failure to achieve haemostasis, vascular rupture, and bleeding diathesis	x	x		x			
Escobar Syndrome (Multiple Pterygium Syndrome):	Multiple pterygia, syndactyly, small stature, camptodactyly Difficulty opening mouth, micrognathia, cleft palate, cardiac defect, fusion of abnormal vertebrae, rib anomalies, joint dislocations, scoliosis, kyphosis, apnea	x	x		x			
Fragile X Syndrome:	Mental deficiency, large prominent ears, macro-orchidism, hyperextensible joints, mitral valve prolapse. High arched palate, prognathism, pectus, scoliosis, torticollis. Behavioral: Lack of co-operation, autism, hypotonia; Cardiac arrhythmias	x			x	x		
Freeman-Sheldon Syndrome:	"Whistling" facies, Small mouth with whistling appearance, high palate, deepset eyes, H-shaped cutaneous dimpling on chin, ulnar deviation of hands, contractures., kyphoscoliosis, Muscle rigidity with volatiles; risk for aspiration, malignant hyperthermia and seizures	x	x	x		x		

NAME	Description	A/irway	Resp	Reflux	CVS	CNS	Liver	Renal
Goldenhar Syndrome:	First and second branchial arch defects, oculoauriculo-vertebral dysplasia, hemifacial microsomia and cardiac defects. Mandibular hypoplasia, craniovertebral anomalies, cleft lip/palate, cardiac and pulmonary complications, renal, CNS defects, laryngeal anomaly, lung hypoplasia	x	x		x	x		x
Kabuki Syndrome:	Growth and mental deficiency, long palpebral fissures, epicanthal folds, tooth abnormalities, Cleft palate, scoliosis, cardiac and urogenital defects, joint hyperextensibility, sagittal cleft of vertebral body, pectus, diaphragmatic eventration Hypotonia, seizures	x	x		x	x		
Klippel-Feil Sequence:	Short neck, low hairline, cervical vertebral fusion. Rib and vertebral anomalies, cardiac and renal defects, cleft palate, scoliosis, deafness, torticollis, unstable short neck	x	x		x			x
Marfan Syndrome:	Tall stature, arachnodactyly with hyperextensibility, lens subluxation, aortic dilatation. Hypertensive response to intubation, aortic incompetence, mitral valve prolapse, diaphragmatic hernia, pneumothorax, cleft palate, scoliosis, hyperextensibility	x	x		x			
Mucopolysac-charidoses: Hunter, Hurler, Hurler-Scheie, Morquio, Maroteaux Lamy and Sanfilippo:	Mucopolysaccharide storage in tissues and organs, coarse features, growth deficiencies. Narrowing of nasopharynx, obstruction of airway, deposition of mucopoly-saccharides in coronary arteries and heart valves, cardiac instability. May have excessive oral secretions	x	x	x	x	x	x	x

NAME	Description	A/irway	Resp	Reflux	CVS	CNS	Liver	Renal
Neurofibro-matosis:	Multiple neurofibromas and cafe´-au-lait spots with or without bone lesions Phaeochromocytoma, laryngeal involvement and RV outflow tract obstruction. Exaggerated responses to muscle relaxants. Kyphoscoliosis, mental retardation, lung cysts, renal artery dysplasia with hypertension, bone cysts, pulsating exophthalmos, sarcomatous changes, spinal nerve compression, laryngeal stenosis	x	x		x	x		
Noonan Syndrome:	Short stature, webbing of the neck, pectus excavatum, deafness, cryptorchidism and pulmonic stenosis Micrognathia, pectus, vertebral anomalies, cardiac defects, lymphedema, cervical ribs, chylothorax, MH	x	x		x	x		
Pierre Robin Sequence:	Micrognathia, glossoptosis, cleft soft palate	x						
Polycystic Kidney Disease:	Cysts in kidneys and possibly liver, pancreas, spleen, lungs (possible pneumothorax), bladder, thyroid. Hypertension, cerebral aneurysm		x			x	x	x
Prader-Willi Syndrome:	Marked obesity, short stature, hypogonadism, mental deficiency, infantile hypotonia, small hands and feet. Diabetes Mellitus, scoliosis. Cardiovascular problems (arrhythmias, conduction abnormalities, PVCs, hypertension), Respiratory problems (restrictive abnormality, dry mouth from viscous saliva), CNS problems (sleep disturbance or apnea, convulsions, thermoregulation disturbance)	x	x		x	x		

NAME	Description	A/irway	Resp	Reflux	CVS	CNS	Liver	Renal
Russell-Silver Syndrome:	Short stature, skeletal asymmetry, cafe´-au-lait spots, clinodactyly. Hypoplastic mandible, renal and cardiac defects, intestine malrotation Risks for malignancies, hypoglycemia, growth hormone deficiency, adrenal insufficiency, excessive sweating / thermal instability	x		x		x		x
Seckel Syndrome:	Severe growth and mental deficiencies, prominent nose, microcephaly, low-set malformed ears. Micrognathia, inability to extend knees, dislocation of hips and elbows, 11 pairs of ribs, facial asymmetry, scoliosis, cleft palate, anemia. Seizures	x	x			x		
Treacher Collins	Malar hypoplasia, downslanting palpebral fissures, lower eyelid defect, ear anomalies & deafness. Mandibular hypoplasia, cleft palate, choanal atresia, cardiac defects	x			x			
Trisomy 13 (Patau's)	Defects of eye, nose, lip & forebrain, polydactyly, scalp lesions, cardiac & renal defects, early death. Cleft lip/palate, cardiac, renal, rib, CNS, colon anomalies, micrognathia, diaphragmatic defect. Seizures, hypotonia,	x	x		x	x		x
Trisomy 18 (Edward's)	Growth deficiency, prominent occiput, small mouth, micrognathia, cleft lip / palate, clenched hands, short sternum, overlapping fingers with low arch dermal ridge pattern, hypertonia, skeletal muscle hypoplasia, short sternum, cardiac, lung, renal, CNS, GIT, rib and vertebral defects. Early death	x	x	x	x	x		x
Trisomy 21	Mental deficiency, hypotonia, flat faces, cardiac defects, slanted palpebral fissures, small ears, hyper-extensibility. Atlantoaxial instability, short neck, cardiac, intestinal, rib defects, hypothyroidism, seizures	x	x	x	x	x		

NAME	Description	A/irway	Resp	Reflux	CVS	CNS	Liver	Renal
Tuberous Sclerosis	Hamartomatous skin nodules, seizures, phakomata and bone.Lesions. Obstructive congestive heart failure, severe and progressive dypsnea, spontaneous pneumothorax, haemoptysis and respiratory failure, hamartomatous brain lesions, renal angiomyo-lipomas, endocrine abnormalities, lesions of oropharynx & larynx- difficult intubation	x	x	x	x	x	x	x
Turner Syndrome	Short female, broad chest, widely spaced nipples, webbed neck, ovarian dysgenesis, congenital Lymphedema. Small mandible,cardiac (usually coarctation of aorta), renal defect (usually horseshoe kidney), rib & vertebral anomalies. Hypothyroidism, hypertension, diabetes mellitus	x	x		x			x
VATER Association	*V*ertebral & rib anomalies, *A*nal atresia, *T*racheo-*E*sophageal fistula, laryngeal stenosis, *R*adial dysplasia, Renal anomaly, cardiac defects, limb deficiency	x	x		x			x
WAGR Syndrome (Aniridia-Wilms Tumor Association):	Aniridia, Wilms tumor, mental and growth deficiencies, congenital cataracts, hypospadias, cryptorchidism. Micrognathia, kyphoscoliosis, cystic kidneys, cardiac defects, blindness	x			x	x		x
Xeroderma Pigmentosa	Sensitivity to sunlight, atrophic and pigmentary skin changes, actinic skin tumors, progressive neurologic problems. Atrophic skin of mouth – difficult mouth opening. Ataxia, spasticity, impaired hearing	x				x		

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