

Autism Dysmorphology Measure (ADM) Training Manual

Chapter I. Introduction

The Autism Dysmorphology Measure (ADM) was developed to provide an efficient and reliable method to identify children with general dysmorphology on physical examination. The presence of significant dysmorphology is an indicator that embryogenesis did not proceed normally. Being able to distinguish the subgroup of children in which embryogenesis went awry from those with apparently normal early development allows us to classify subgroups of children that differ for an etiologic indicator.

The assessment of dysmorphology is one of two components used to define complex autism; the second is microcephaly. Complex or more precisely complex neurodevelopmental autism is defined as autism for which there is evidence for an etiologic start point during embryogenesis, roughly from 2 to 12 weeks gestation. Essential autism comprises the remainder of individuals whose early development appears to have proceeded normally.

Based on examination of approximately 300 children with autism, we determined which physical features most consistently distinguished children with general dysmorphology from those with normal examinations. Using the Classification and Regression Tree (CART) statistical method we developed a sequential algorithm to separate dysmorphic from non-dysmorphic children with high specificity and sensitivity. The result is the Autism Dysmorphology Measure (ADM) which directs a standardized assessment of dysmorphology for 12 key body areas; following the sequence of the algorithm the individual is classified as dysmorphic or non-dysmorphic.

Theoretically, the process is straight forward and fast. The complexity comes in defining the rules by which the scorer will consistently code each of the 12 body areas as normal or dysmorphic. Medical Geneticists and dysmorphologists spend years in training and practice learning how to assess physical dysmorphology. This is because there is no absolute “normal” for each feature; some features are continuous, such as from small to big and others vary considerably between families and ethnic groups. The key to the efficacy of the measure is standardization of the assessment of each of the 12 body areas. This training manual will instruct the clinician in this assessment process.

This training manual includes a written guide to scoring the 12 nodal body regions used in the ADM algorithm and a picture of a normal structure. The nodal body regions represent discrete entities with explicit rules that must be fulfilled to score each region. These descriptions and pictures can be compared with the study subject. It is designed to be clear, simple, without anatomical jargon and useful for clinicians not trained in dysmorphology. It is also recommended that each learner have a copy of either Smith’s Recognizable Patterns of Human Malformation or Aase’s Diagnostic Dysmorphology.

Chapter II. Significance and History

Physical anomalies are well recognized indicators of an insult, genetic or environmental, occurring in the first trimester (Smalley et al, 1988); their presence or absence can be used as an indirect measure of events during embryologic development. Physical anomalies are described as major or minor. Major malformations, such as congenital heart defects and facial clefts, reflect abnormal development; however they occur infrequently and when they occur in isolation, only tell us that that one organ system was affected. Minor physical anomalies, on the other hand, occur frequently in populations. They are not medically of great consequence, but taken together, they provide evidence of developmental dynamics negatively affecting morphogenesis. In other words, we use the sum of minor

anomalies as an indicator of embryologic well being or distress. Though the terms malformation and anomaly are synonymous, convention is to use the terms major malformations versus minor anomalies.

These principles have been used by medical geneticists and dysmorphologists starting in the 1960s to define hundreds of genetic and environmental syndromes which leave characteristic morphologic footprints (Jones, 2006, OMIM, 2007). The presence of multiple minor anomalies distinguishes children who are at increased risk for both major malformations (Marden et al, 1964, Mehes et al, 1973, Smith, 1982, Leppig et al, 1987) and behavioral disorders including autism (Waldrop et al., 1973, Mnukhin and Isaev, 1975; Campbell et al, 1978; Walker, 1977; Links, 1980; Links et al, 1980; Steg and Rapoport, 1975; Gualtieri et al, 1982). Walker, using the Waldrop weighted scoring scale (Waldrop & Halverson, 1971) for 16 anomalies, studied 74 autistic and non-autistic children matched for age, sex, socioeconomic group and geographic domicile, and found that the mean minor anomaly score of 5.76 for the autistic children was significantly higher than the control group score of 3.53. He concluded that this shift to a greater number of anomalies in the autistic subjects proved organicity in autism. Rodier et al. [1996, 2002] proposed that physical phenotypic features could be used to pick out the children whose autism was due to mutations in the embryologically important homeobox genes that model the development of the brain stem and face. They also surmised that environmental teratogens including valproic acid and thalidomide produce teratogenic phenocopies by influencing the same early developmental pathways. In 2000, we proposed that the accumulation of minor physical anomalies defined a subset of children with autism (Miles & Hillman, 2000). Subsequently, we defined complex autism as the individuals in whom we recognized evidence of a fundamental fault in early morphogenesis, define by either significant dysmorphology or microcephaly (Miles et al., 2005). Microcephaly is easy to diagnose; dysmorphology is not.

The complex subgroup comprises about 20% of the total autism population studied and in our studies individuals with complex autism have poorer outcomes with lower IQs, more seizures, more abnormal EEGs (46% vs 30%) and more abnormal brain MRIs (28% vs 13%). The remainder have essential autism which is more heritable with a higher sib recurrence (4% vs 0%), more relatives with autism (20% vs 9%) and a higher male to female ratio (6.5:1 vs 3.2:1). These group differences between individuals with complex and essential autism were predicated on the developmental principle that individuals for whom there is evidence of an insult to morphogenesis will be etiologically distinct from those whose development proceeded normally and can be expected to differ in outcome and genetic measures.

To classify individuals as dysmorphic, we performed complete, unclothed examinations, scoring more than 500 single features and classified individuals as dysmorphic if they had 6 or more abnormal dysmorphic features. In our hands, this technique allowed medical geneticists to classify individuals with good reliability and validity. We deemed this approach inefficient for most clinicians working with autism. Moreover, we recognized that developing a measure of general dysmorphology is much different than describing the specific features that define a disorder such as Down syndrome. In that case cluster analyzes are helpful in defining the most informative features. By listing the features and calculating sensitivity and specificity it is straightforward to develop a diagnostic algorithm for Down syndrome. Autism, however, is an etiologically heterogeneous behavior disorder for which there are more than 50 described discrete causes, in addition to an even larger number of chromosome abnormalities (OMIM, Genetests). Defining a dysmorphology scoring measure for autism is analogous to defining a measure of dysmorphology for mental retardation where throwing out any specific feature is difficult to justify. Based on these considerations and the fact we achieved better validity when dysmorphology was coded by body regions we adopted a system that allows the clinician to code body regions as dysmorphic or non-dysmorphic, rather than counting individual minor anomalies.

Using Classification and Regression Tree methods (Breiman, et al, 1984) we developed the autism dysmorphology measure (ADM) to provide clinicians a practical way to distinguish individuals with

complex autism from essential autism. It was designed to lessen the dependence on “expert” clinical judgment and to allow the clinician to rely more on comparison with normal structures. The ability to obtain this information from a clothed exam is more practical with noncompliant children. Research benefits will come from identifying both the more genetically homogeneous essential subgroup and by identifying dysmorphic individuals whose complex autism is less heritable and more apt to be due to sporadic mutations, including point mutations, deletions, insertions, duplications and other chromosomal rearrangements. Since, virtually all the identified autism syndrome diagnoses are made in individuals with complex autism, it is anticipated that emerging technologies like oligo-microarrays will be more informative in this subgroup.

We recognize a number of caveats to reducing the complex process of the full dysmorphology examination, based on understanding the embryology, to a relatively simple algorithm. The first concern is how to reliably and consistently differentiate dysmorphic from non-dysmorphic for physical features whose structure and size are along a continuum. This is of course the challenge for all diagnostic measures whether it is defining abnormality of an MRI, EEG, or a behavioral measure of autism core symptoms. Since this algorithm reflects experience with children with autism, we hope the definitions on which it was based will continue to hold true.

Second is the concern that some individuals may have dysmorphology limited to areas not assessed by the ADM algorithm. That is certainly going to happen and it must be noted that the ADM is not intended to replace a general medical examination intended to detect known causes of autism, such as Tuberous Sclerosis, Fragile X syndrome, Timothy syndrome and PTEN disorders. When significant dysmorphology is noted, a comprehensive examination by a trained and experienced dysmorphologist will continue to be the gold standard and should guide decisions on diagnostic laboratory tests.

The third caution is that we don’t yet know how the measure will perform when used by clinicians who are not trained in dysmorphology. Our validity and reliability study will compare the performance of dysmorphologists with other medical clinicians with varying degrees of training in children from different ethnic backgrounds. This study is necessary to establish the usefulness of the ADM and determine the type and extent of instruction needed for a range of clinicians and scientists to use the measure successfully.

Chapter III. Dysmorphology Primer

Learning about dysmorphology can be approached from a number of paths. The most satisfying is based on embryogenesis and how both genetic and environmental insults lead to structural deviation. That unfortunately is beyond the time investment for most autism clinicians whose goal is to identify children who are generally dysmorphic. It is also outside the scope of this manual. The interested reader is encouraged to investigate these references (Aase, 1990, Jones et al., 2006, Winter and Baraitser, 1996, Hall et al., 2007, Ferretti et al., 2006). A second path is to learn to identify specific malformations and then research what is known of the etiology and prognosis. This may be an adequate approach for the clinician who specializes in a specific organ system such as the heart or the urogenital system. However, it is not efficient or practical for assessing large numbers of children with pervasive developmental disorders in a busy clinical setting. The approach of the ADM training is to learn to identify the abnormal by comparing body structures to normal. Defining normal will be the greatest challenge. Using the ADM requires the evaluation of 12 structures, some of which are easy to score. Height, for instance relies on measurement and comparison to charts normed by age and gender. Others depend on ruling out obvious malformations, such as an extra finger or a bent toe. For those we will rely on descriptions and pictures of commonly observed anomalies. The remainder will be more difficult as abnormality represents one end of a continuum from normal into abnormal, such as a large nose. For these we will depend on comparing the child’s features to those of his/her parents who don’t have autism. This requires careful observation and description.

But first it is necessary to construct a framework in which to think about and describe dysmorphology. What is the difference between a birth defect, a malformation, an anomaly, and a deformation? Learning these concepts will help you describe what you are seeing.

Comfort with the definitions will provide a good basis for understanding exactly what dysmorphology is and why it has been so useful in the delineation of thousands of genetic and environmental syndromes.

Principles

By the beginning of the fetal stage (week 8) of development, after embryogenesis (week 4 – 7), the human form has achieved complete differentiation of organ systems. The remainder of fetal development is primarily a period of growth. Abnormalities in embryogenesis result in what are commonly called birth defects. Recognizing when birth defects occurred provides critical information to the medical geneticist who is working to identify the etiology, the physician who needs to know if the patient has additional cryptic anomalies, and the scientist who is attempting to identify the various causes of autism.

Classification and Definitions

Dysmorphology: study of human congenital structural abnormalities.

Birth Defect: common name for a congenital structure abnormality. Significant birth defects that interfere with normal functioning occur in about 3 % of children.

- Birth defects may be due to a malformation, a deformation or a disruption.
- The terms birth defect, anomaly and structural abnormality are used interchangeably.

Malformation: structural anomaly that is caused by abnormal formation of the embryo. Early development may be misdirected, delayed or arrested.

- Malformations may affect one organ system, an anatomic region such as the face or affect multiple body systems.
- Malformations may be major or minor

Deformation: structural anomalies caused by mechanical forces that distort otherwise normal structures. For instance, a fetus confined to a structurally abnormal uterus may have bowing of limbs caused by crowding of an embryologically normal structure. The key to identifying a deformation or disruption is that the birth defect does not conform to what is expected from an interruption of embryological development.

Disruption: structural anomalies caused by destruction of previously normal tissue. For instance, loss of blood supply (ischemia) to a limb may cause loss of a hand or an amniotic band may amputate a fetal limb.

Major Malformation: affects a medically important structure such as the heart, kidneys, brain or palate.

- Most major malformations are isolated defects
- Most major malformations can also occur as part of a syndrome of generally disordered morphogenesis
- For instance, 90% of congenital heart defects are isolated and 10% are part of syndromes.

Minor Anomalies or Minor Malformations: anomalies that occur in less than 4% of the population and are of no serious medical or cosmetic consequence.

- Terms minor malformation and minor anomaly are used interchangeably
- Minor external anomalies are found most commonly in body structures that are embryologically complex, such as the ears, face, hands & feet. (get Marden graph)
- Common examples include:
 - * Flat Philtrum
 - * Thin upper lip
 - * Single palmar crease (3.7% of newborns, 2 males: 1 female)
 - * Clinodactyly of 5th finger of >8°, caused by hypoplasia of the middle phalanx which is the last digital bone to develop
 - * Clinodactyly of other fingers and toes
 - * Abnormal dermatoglyphics including a distal axial palmar triradius, open hallucal area, high frequency of whorls (> 8 in 3% nl) or arches (>6 in 0.9% nl), radial loops on fingers 4 and 5 (1.5% nl)
 - * Abnormal nails

Normal Variants: Features that occur in more than 4% of the population and are often familial and should not be classified as anomalies. There is nothing magic about the 4% cut off, though previous studies suggest it is a reasonable indicator of which variations of development are or are not likely to be associated with additional anomalies, mental retardation or major malformations. There is a gray area between normal variants and minor anomalies so most geneticists will note the “normal variants” observed during an exam. Often the distinction between a normal variant and a dysmorphic feature is one of degree, as in mild 2-3 syndactyly (a normal variant) versus moderate 2-3 syndactyly (a minor anomaly).

Common examples

- Stork bite mark in infants
- Mild 2-3 syndactyly of toes in infants
- Shallow sacral dimple
- Darwinian tubercle of the ear helix
- Incompletely over folded helix in infants
- Brushfield spots of the iris in newborns (20% nl newborns)
- Central post hair whorl (14%)
- Mild frontal upsweep of the hair (5%)

NB. Aase (1990) sometimes uses the term “minor variants” rather than “minor anomalies”.

Dysmorphic Feature: This is a general term for a morphologic abnormality that is outside the normal range of development either by descriptive observation or measurement. Sometimes used synonymously with a minor anomaly, but more accurately would include any malformation.

Syndrome: When a particular set of anomalies occurs together with some frequency it is termed a syndrome. Syndromes range from the very common and well verified like Down Syndrome to the rare such as Miles-Carpenter Syndrome which has only been reported in one family. Geneticists may refer to a collection of anomalies in an individual as “syndromic” which only means, based on their experience, similar collections have turned out to occur together as a syndrome.

Chapter IV. The Dysmorphology Examination

Approach

Three strategies will be used to distinguish truly abnormal from irrelevant descriptive features observed in the examination of a child with autism. The first is a keen sense of what “looks” normal and what appears somehow different or odd. As in all diagnostic endeavors, an experienced clinician can best decide where to draw the line between normal and abnormal. This holds for determining

whether a febrile child is “seriously ill” as in meningitis, whether a child’s behavioral symptoms are marked enough to qualify as autistic disorder, and whether a body system is dysmorphic. Thus, experience and simple comparisons to normal will be the first approach. The second is to use one of the major dysmorphology references (Aase, 1990, Jones et al., 2006, Winter and Baraitser, 1996). Their descriptions and pictures provide examples that can be compared with the study subject. The third is to compare the child to his or her parents. For instance, a large nose in a family with familial large noses is not a significant breach of normal morphologic development.

1. ADM Examination Instructions: (Appendix 1 – Work sheet)

The examination is designed to be done with the child clothed, which makes it practical for children who are wary of touch, but can be done in the context of the medical and neurologic examinations. Access to both parents is important and if only one of the parents is present request submission of photographs that show facial features, hands and feet.

a. Equipment requirements: The physical dysmorphology examination is performed in a clinic equipped with: medical scales, standing height measure, non-stretchable measuring tape or a 6 inch transparent plastic ruler, plastic protractor, one or more hair clips to hold hair back off the ears, and a digital camera.

b. Measurements: Height, weight, head circumference, ear length, inner canthal distance, outer canthal distance, hand length, palm length, foot length. Look up % for age & gender (Appendix 3). We will define measurement of < the 3rd percentile and > the 97 percentile as abnormal.

c. Assess each of the 12 Body Systems: Grade each body area as normal or abnormal. A list of dysmorphic features noted in a population of children with autism with general dysmorphology is provided for reference. The list is not exhaustive however and is best used to jog memory of things to consider. The feature guide in Chapter VI provides a more in depth reference.

d. For each abnormal feature, examine both parents to determine whether they have the feature. If a feature is present in one of the parents, and the parent does not have a pervasive developmental disorder, that feature is considered normal for the family.

e. Mark the ADM algorithm and follow the nodes till you reach either non-dysmorphic or dysmorphic.

2. How to deal with malformations not assessed by the ADM

The ADM was developed by the medical geneticists comparing children with autism who they considered “dysmorphic” with children with autism who did not appear dysmorphic. Since it is based on a limited population of children, uncommon birth defects and malformations are not captured in the algorithm. For example, none of the children had a cleft of the nose, which is rare and usually part of a cleft lip. Thus, scoring nose malformations is not statistically of use for a short dysmorphology measure for children with autism. This does not mean, however, that a nose malformation is irrelevant or should be ignored. Obvious malformations or birth defects should be noted and should prompt referral to a medical geneticist who will determine whether the malformation is an isolated defect or part of general dysmorphology.

Major birth defects such as cleft lip &/or palate, congenital heart defect or spina bifida are usually isolated (~80-90%) and unrelated to the autism. However, they may be part of a syndrome of generalized dysmorphology. All children with major birth defects should be evaluated by a medical geneticist as well.

Suggested General Examination Protocol for ASD

The physical examination of a child being evaluated for autism should be done by a medical clinician who is knowledgeable of autism and whose goals are to 1) verify the health of the child and identifying acute or chronic health problems that may interfere with optimum progress, 2) identify underlying disorders that are known to cause autism, such as Fragile X syndrome, 3) identify autism endophenotypes including generalized dysmorphism, microcephaly and macrocephaly. The medical examination includes the medical history, review of systems and family history. Histories of birth defects, serious or chronic illnesses, surgeries, growth problems and family histories of disorders all inform us of things that may affect general well being, prognosis and response to therapies.

1. General Autism Medical Examination

- a. Record height, weight and head circumference & plot on age appropriate growth charts.
- b. Thorough physical examination and review of systems.
- c. Dysmorphism evaluation, noting minor or major anomalies. In clinical practice this can be a comprehensive dysmorphism examination performed by a medical geneticist or just the ADM to assess for generalized dysmorphism.
- d. Look specifically for features that occur in recognized autism related syndromes. This list will undoubtedly grow as additional disorders are recognized.
 - 1) Fragile X syndrome – macrocephaly, ligamentous laxity, macro-orchidism
 - 2) Tuberous Sclerosis – facial fibrous angiomatous lesions (adenoma sebaceum), hypopigmented macules including ash leaf spots and confetti hypopigmentation, shagreen patches/orange peel spots, periungual fibromas. Requires a Woods lamp.
 - 3) Timothy Syndrome – finger syndactyly,
 - 4) Sotos Syndrome – macrocephaly, broad forehead, large hands and feet
 - 5) PTEN mutations – pigmented nevi on the penis or scrotum
 - 6) Moebius syndrome – facial weakness making it impossible to smile, usually asymmetric. Inability to fully abduct the eye (all the way laterally)

Chapter V. Photography for the ADM

Photographing small children can be a challenge and generally requires help from the parents.

Some techniques that may be helpful:

- Have pictures on the wall behind you or someone behind you to hold the child's attention.
- Set the digital camera to take a continuous series of photos.
- Set up the camera on a tripod aimed at the child with a remote that you can use at any time during the visit.
- Use a blue wall.
- Don't shoot into the light.
- To document something you are calling abnormal get multiple angles.

Face (includes nose, ears, mouth, teeth, philtrum)

Frontal – full face with the subject looking directly at the camera not smiling or grimacing. Eyes normally open.

Frontal with mouth open to get teeth. Photographing teeth is less important and often just documented by observation.

Side view (from both sides) – Hair held back with a clip to give a good view of the ear. The face should be facing straight and the line from the brow ridges to the lower maxilla should be vertical.

Hair

If the hair pattern is abnormal document photographically.

Hands

Have the child put his/her hands on a fixed object, like a chair or stool. Take picture from above. Do both palms up and palms down with fingers mildly spread.

Feet

Have child stand on the floor with pants pulled up and shoot from above and from the side

Chapter VI. Guide to scoring the 12 ADM nodal body systems

For each of the 12 nodal systems this guide will outline important landmarks to use in describing the structure, examination techniques, embryology of the area, a list of common anomalies, any common normal variants and problematic calls or gray areas. The list of anomalies for each node is not inclusive or exhaustive.

Keep in mind that the objective is to pick out malformed structures. Thus, the examiner will often be expected to make the distinction between minimal vs marked abnormalities. For instance, a relatively long face, especially in a teenager would not be counted whereas a markedly long face would. Just as with the DSM-IV, experience makes the decisions easier.

The rules for the ADM are to make the best decision you can, following the scoring criteria as precisely as possible. When gray areas arise that affect the final score, the result can be equivocal. In our experience, equivocal calls are usually best placed in the non-dysmorphic category. However, when this measure is used in patient care clinics, children with equivocal results would best be served by referral to medical genetics.

Though potentially misleading, I recommend starting by studying the shape, structure and relative size of your own body parts scored in the ADM. Remember that one minor anomaly doesn't mean much on its own and it makes a great teaching tool.

1. Short Stature

Significance embryology: Growth failure is one of the sentinel findings in children with generalized dysmorphism. It may occur either prenatally or postnatally. Short stature is common in many single gene disorders and most chromosome disorders. Children with chromosome disorders, regardless of which chromosome segment is duplicated or deleted, generally have growth retardation, mental retardation, generalized dysmorphism and premature death. This makes sense when one considers that chromosome disorders are caused by aneuploidy for multiple genes and each feature (brain development, growth, physical features and health) is controlled by multiple genes scattered throughout the genome.

Examination technique: Measurement is done recumbent on an infant scale until 18 months of age and thereafter standing.

Cut off: Height <3rd centile is abnormal.

Gray Areas:

- a. Faced with a growth curve indicating prenatal or early growth retardation (<3%), followed by catch up to only around the 10th centile, especially if the parents are tall, would lead to an abnormal designation.
- b. The differential for growth retardation includes general health problems, such as cardiac, renal or endocrine diseases. Fortunately in autism this is not usually the case, but when children with short stature are identified they should be referred to a pediatrician for medical assessment.

2. Hair Growth Patterns

Significance & embryology: Scalp hair distribution provides important clues to early development. The hair bulb forms at 14 weeks and the growth of the scalp, which is strongly influenced by brain growth, stretches the hair shaft from its original perpendicular orientation to more vertical, so the hair “lies down” and doesn’t “stand on end”. Brain growth doesn’t exert a uniform pull on the skin and the most rapidly growing area, between 16 to 19 weeks, is capped by the posterior hair whorl. Generally it is off center and back at around the position of the posterior fontanel. The third influence is the suppression of hair growth in a circle around the face, around the ears and less distinctly along the back of the neck. Finally, the posterior hair line is influenced by growth of the neck or neck edema. This is commonly observed in Turner syndrome where prenatal swelling of the neck occurs due to dysplasia of the lymphatics which usually recovers by the end of gestation. The result is a wide neck, a low posterior hair line and upsweep of the hair line.

Examination technique:

Look at the child from the front, the back and from above, noting the hair lines, hair whorls and cowlicks.

Abnormalities:

- a. The position of the posterior hair whorl is not exact, but multiple hair whorls, widely spaced (>3cm) double hair whorls, markedly displaced hair whorls or no posterior hair whorl are abnormal.
- b. A frontal cowlick is an accessory hair whorl and though relatively common it indicates a subtle alteration in fetal brain growth. A marked upsweep, especially in conjunction with other hair growth pattern abnormalities is abnormal.
- c. A low anterior hairline especially approaching the lateral eyebrows is abnormal.
- d. A widow’s peak is seen in patients with hypertelorism and reflects a lack of hair suppression around the eyes as they are laterally displaced. A marked widow’s peak is abnormal.
- e. Upsweeps of the posterior hair line or slightly low posterior hair lines are common and if not pronounced are considered normal variants.

Normal variants:

- a. A central hair whorl which occurs in 5% is a normal variant.
- b. A mild frontal upsweep which occurs in 15% of people is a normal variant.

3. Ear Structure, Size and Placement

Significance and embryology:

The ear is embryologically complex, formed from three converging tissue planes. The external ear develops from the six swellings called the auricular hillocks, which arise around the first branchial groove. Near the end of embryonic period, the external ear forms from zones of the first and second branchial arches and migrates up and laterally from its original position near the middle of the mandible. Failure to complete this migration leads to an ear that is low set and posteriorly rotated.

Examination technique: Includes assessment of size, placement (position & rotation) & structure.

- a. Measure the length of the external ear (pinna) from the top of the helix curve to the bottom of the lobe. Plot on a standard curve. If the helix is over folded do not unfold to measure.
- b. Determine position of the ear. The head must be held erect with the eyes facing forward and the facial profile vertical when viewed from the side. There are a number of ways of measuring ear position from either the side or front. Using two simple methods together works well. Both depend on relatively normal placement of the eyes.

1st From the side, draw an imaginary line from the outer canthus of the eye to the most prominent part of the occiput. The upper point of attachment should be above or on the line.

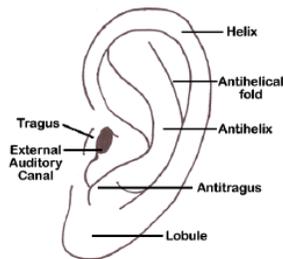
2nd From the front, draw an imaginary line through the inner and outer canthi and extend laterally. The most superior point of attachment should be above or on the line.

c. Determine rotation of the ear. The head must be held erect and vertical. Imagine the line connecting the outer canthus of the eye and the most prominent point of the occiput. Then imagine a line perpendicular from the top of the head to the top of the helix. The angle of rotation of the ear is that subtended between the vertical axis and the longitudinal axis of the ear. Normal range is 10 to 30 degrees.

d. Determine protrusion of the ear. The simplest method is to measure the greatest linear distance between the external ear and the temporal region of the skull. Protrusion is considered excessive if the measurement is more than 2 cm.

e. Look for abnormalities of the preauricular regions (tags, pits, fistulae), helix (front & back), antihelix, tragus, lobe, external auditory meatus.

Figure: landmarks of the external ear



Abnormalities:

- a. Long (> 97%) or short (<3%), or tiny & malformed (microtia)
- b. Low set
- c. Posteriorly rotated
- d. Protruding or cup ear (defect in posterior auricular muscle)
- e. Lop ear (defect in superior auricular muscle)
- d. Crumpled ear (intrinsic ear muscles), over folded helix
- e. Pits, grooves or creases on back of the helix
- f. Absence of the superior or inferior crus
- g. Large tragus or antitragus, especially if the size or position is asymmetrical
- h. Preauricular pits, tags, fistulae
- i. Narrow or atretic auditory canal

Normal Variants:

- a. Attached lobe (~20% Caucasians)
- b. Darwinian tubercle

Gray Areas/ Pit falls:

- a. The most critical step in assessing the position and rotation of the ear is holding the head in a true vertical position. Subjective assessment is notoriously inaccurate.
- b. Ear structure is often familial.
- c. African Americans are more apt to have familial anomalous pinnae.
- d. Both ears should look alike.
- e. Intrauterine pressure can retard ear growth.

4. Nose Size

Significance & embryology

Nose shape and size are extremely variable, familial and related to family origin. Only nose size is assessed for the ADM. Wide nasal bridge and wide spaced eyes reflect midline development and appear to be common in essential as well as complex autism. Most nasal malformations like a bifid tip or a cleft nostril are rare.

Examination techniques

Look at the nose from the front and assess the length and width relative to the rest of the face. For the ADM measurements are not required. There is such variability in nose shape the differences in measured size are difficult to interpret. Thus, the scoring is subjective and takes into account width of the nasal root and length.

Abnormalities

- a. Large nose – includes a wide root, bulbous tip or a long nose. A broad and high nasal bridge gives a tubular look to the nose.
- b. Small nose – all of the above can be small.

Normal variants

- a. Variation is the rule and is assessed by comparisons with the family.

Gray areas & pitfalls

- a. Nasal bridge is cartilaginous and becomes more prominent with age.
- b. There are few disorders that cause ASD symptoms, are variable enough to be missed in a parent and affect nose size. Velo-cardio-facial /CATCH 22/ 22q- syndrome is one. This syndrome causes a large and bulbous nose, tapered fingers, developmental delays that range from mild to severe and schizophrenia and other psychiatric symptoms. The deletion of 22q21.1 will be picked up on the microarray.

5. Face Size and Structure

Significance and embryology

The face is embryologically complex with contributions from the neural crest, mesoderm and branchial arches. How the lateral structures come together and meet in the midline is influenced by the underlying brain. Facial proportions change with age with more than half of the newborn face being forehead, reflecting the proportionally large brain. With age the mandible, the midface and maxilla as well as cartilaginous features such as the nasal bridge enlarge disproportionately. The mentum is the midpoint of the mandible and marks the center of the chin. Facial size and proportions are also influenced by gender as the male facial skeleton is bigger and coarser. Deformation of the face can occur prenatally or result from premature fusion of a cranial suture.

Examination Techniques

Inspection is the only way to assess general facial dysmorphology. Look from a number of angles locating the landmarks for reference. Since there is tremendous variation in facial size and structure this is an area where parental comparisons are important. If you still aren't sure after examining the parents or if they insist the features are just like their childhood features have them bring in early photographs for review.

Landmarks: Brow ridge, zygomatic arches, midface, chin, facial plane depicted on the lateral view by a plane transecting the prominence of the brow ridges and lower maxilla.

Normal faces



Abnormalities

a. Size

- 1) Small face refers to the area of facial features and is usually compared to the size of the skull. They may appear pinched as in Johansson-Blizzard syndrome, flat as in Down syndrome, or crowded together in the middle of the face.
- 2) Thin face as a measure of structure, not nutrition.
- 3) Long face, usually associated with both a long upper face and a long jaw.
- 4) Coarse features are age and gender dependent. Coarse facial features make young children appear old for their age. Older children appear unattractive.

b. Structure

- 1) Asymmetric face is a frequent feature in dysmorphology syndromes but can also be part of a neurologic or muscle disease. It is often not noted until you ask the child to smile. Being alert to facial asymmetry will help identify Moebius syndrome.
- 2) Flat face is best judged from the side where the plane of the face and features are all in a straight line.
- 3) Mid-face hypoplasia is due to an underdeveloped maxilla. It gives a dished-in face.
- 4) Flat malar region is similar and often misclassified as midface hypoplasia. It is due to underdevelopment of the zygoma.
- 5) Triangular face exhibits disparity between the broad forehead and narrow jaw to give a pixie look.
- 6) Prognathism/prominent mandible is usually easy to spot. It is often familial. Prognathism is characteristic of Sotos syndrome which is an autism related disorder.
- 7) Micrognathia/small mandible. Mandible is recessed and is sometimes associated with a midline submucous cleft of the palate. The association between micrognathia, a midline cleft palate and glossoptosis is called Pierre Robin sequence.
- 8) A dimpled, grooved or markedly pointed chin is abnormal. Scoring depends on degree and parental comparison.

Gray areas & pitfalls

Scoring abnormal facial structure is age, gender and family dependent. Young children have fine features, a lower nasal bridge and small jaw compared to adults.

6. Philtrum

Significance & embryology

The philtrum is the central groove and lateral pillars that extend from the base of the nose to the vermilion border of the upper lip. The groove indents the upper lip to form the cupid's bow. Children with Fetal Alcohol Syndrome classically have a flat smooth philtrum with a thin upper lip. Astley and Clarren (1995) developed a 5 point Likert scale to judge the smoothness of the philtrum and the thinness of the upper lip with a 5 being the most abnormal. A relationship to brain growth is suspected but not proven.

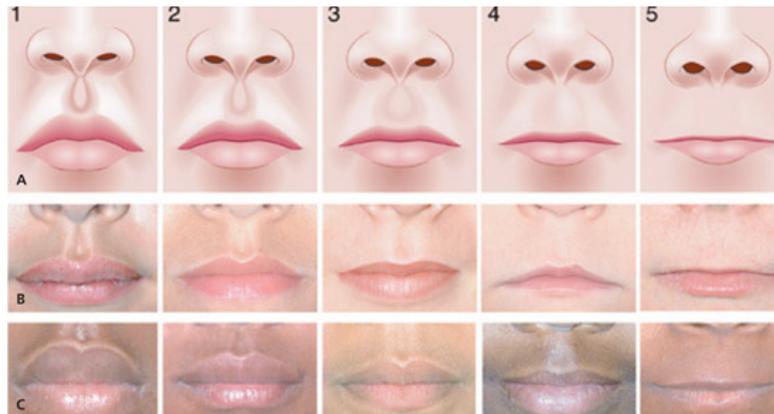
Examination techniques

- Length – Tables for philtrum length are available (Hall et al., 2007) and show the greatest growth in the first 2 years of life. I rarely find them helpful as the “normal range” is broad. The normal philtrum length for a child is about 1 1/4 cm; less than 3/4 cm generally looks short and is often associated with a pulled up or tented upper lip.
- Structure is by observation. The Astley–Clarren scale (*appendix x*) assesses the transition to smooth with a thin upper lip.

Figures



Flat philtrum, thin upper



FLip-Philtrum Guide. (A) The smoothness of the philtrum and the thinness of the upper lip are assessed individually on a scale of 1 to 5 (1 = unaffected, 5 = most severe). The patient must have a relaxed facial expression, because a smile can alter lip thinness and philtrum smoothness. Scores of 4 and 5, in addition to short palpebral fissures, correspond to fetal alcohol syndrome. (B) Guide for white patients. (C) Guide for black patients. From Wattendor & Muenke, 2005

Abnormalities

- Smooth/flat philtrum is abnormal
- Long philtrum is abnormal, though mainly when associated with a flat philtrum.
- Short philtrum is abnormal.
- Prominent philtrum with a deep philtrum groove is abnormal.

Gray areas & pitfalls

- Smiling alters the philtrum so examination and photographs should be with a neutral expression.
- The philtrum and upper lip often change together, such that a flat philtrum is associated with a thin upper lip with a poor vermillion border.
- Length of the philtrum varies inversely with the length of the nose. A long philtrum may reflect a short nose and a short philtrum a long nose.
- Children with Fetal Alcohol Syndrome can be diagnosed with an ASD and long smooth philtrum should prompt looking for other FAS signs including microcephaly, short palpebral fissures and distal digital hypoplasia based on finger tip arches &/or small nails.

7. Mouth & Lips

Significance & embryology

The structures surrounding the oral cavity originate from the maxillary and mandibular portions of the first branchial arch (skeletal), and the regional mesenchyme (muscle & soft tissues). Children with syndromes commonly have abnormal size and shape to the mouth. A small mouth is usually a first branchial arch abnormality and may look like an O. A large mouth may be symmetrical or caused by a cleft extending toward the ear caused by failure of the lateral mesenchymal masses of the maxillary and mandibular prominences to merge.

Lip abnormalities range from a thin upper lip usually lacking a cupid's bow and associated with a flat philtrum to prominent lips, usually in the lower lip. The vermillion border is a transition tissue between skin and mucus membranes

Examination techniques

The mouth and lips can be evaluated by inspection. Look for size, symmetry and shape of the structures.

- a. Size – observation and comparison to surrounding structures.
- b. Shape – observation with mouth at rest.

Abnormalities

- a. Small or large mouth size is abnormal
- b. A down turned or carp shaped mouth is abnormal
- c. A prominent, protruding lower lip is abnormal
- d. Clefts are abnormal
- e. Pits in the interior of the lower lip may be associated with fistulas to small accessory salivary glands and are abnormal. They occur in the clefting disorder Van der Woude syndrome. Lip pits at the corners of the mouth are minor anomalies.

Normal variants

- a. Relative macrostomia or microstomia and thick or thin lips may be family characteristics.

Gray areas & pitfalls

- a. Distinguish between abnormal structure and low neurologic tone or muscular weakness.

8. Teeth

Significance & embryology

The teeth appear as buds of ectoderm extending down into the mesenchyme of the early mandible and maxilla at around week 6. Each incisor develops from three closely spaced growth centers that normally fuse together before eruption, but usually leave irregular borders on the incisors in young children. Defects in these growth centers lead to abnormal tooth shape and size. Common abnormal shapes of teeth include notched incisors, shovel teeth where the lateral edges curve medially and mulberry molars that are spherical with distortion of the cusps. Notched incisors are due to a defect in the incisal edge, narrow incisors may be due to absence of one of the growth centers and fused teeth are due to tooth bud fusion. Taurodontia may affect all or some of the molars and is characterized by elongation of the body of the tooth producing large pulp chambers and small roots. Taurodontia is described in a number of chromosome abnormalities.

Examination techniques

Inspection and counting of the teeth is sufficient.

Abnormalities

- a. Absent teeth / hypodontia/ oligodontia can be an isolated anomaly but often runs in families as a dominant trait.
- b. Supernumerary teeth erupt from the primary palate, just behind the upper incisors.
- c. Small or narrow teeth are abnormal.
- d. Large teeth are abnormal and may be seen in a number of syndromes
- e. Aberrant tooth morphology including peg or conical of teeth and Taurodontia are abnormal.
- f. Bigeminal or fused teeth are abnormal.

Normal variants

- a. Oligodontia is quite common and is sometimes considered a normal variant. But in the ADM it is coded as an abnormality.

Gray areas & pitfalls

- a. Enamel defects such as pits, grey teeth, carious teeth are not malformations.

9. Hand Size

Significance & embryology

The arm buds appear at the beginning of the 5th gestational week. By the end of that week paddle shaped hand and foot plates and segmentation of the digital rays is beginning. The leg buds lag a few days behind the arms.

Examination techniques

- a. Hand length is measured along the palmar surface from the most distal wrist crease to the end of the middle finger. The measurement is compared to the age chart. Greater than the 97% is large and < 3% is small.
- b. Width measurements are not helpful. General inspection of width is useful.

Abnormalities

- a. Large hands >97%
- b. Small hands <3%

Normal variants

- a. Familial patterns and relation to height are taken into account.

10. Fingers & Thumbs

Significance & embryology

By the end of the 8th week of gestation the digits have separated producing quite a mature appearing hand. The palms and finger tips have soft tissue pads, the growth of which determines the dermatoglyphic patterns. Finger movement starts by week 12 to establish palmar and interphalangeal creases which can be seen by the 20th week. Abnormal hands, including the fingers and thumbs, are commonly abnormal in general malformation syndromes.

Examination techniques

- a. Inspect the fingers from the palmar and dorsal surfaces, with fingers slightly apart for polydactyly, syndactyly, camptodactyly, abnormal finger shape.
 - 1) Polydactyly is usually post axial/ ulnar. It ranges from a complete extra finger, which would have been removed shortly after birth to a nubbin of skin on the lateral side of the hand.
 - 2) Syndactyly is usually obvious, though mild syndactyly may be missed especially looking at the palm of the hand. Mild syndactyly pushes any rings up toward the proximal interphalangeal joint.
 - 3) Fingers should easily open to 180°.
 - 4) Fingers should be slightly tapered with slight, undulating curves around the joints.
- b. Finger lengths should be symmetrical. Short fingers may be due to short phalanges or short metacarpals. Inspection is usually sufficient, especially if all fingers are not uniformly shortened. Looking down on a fist hand allows easy visualization of the metacarpal lengths. Tables for length of the middle finger from the proximal crease to the tip of the finger are available, but not usually necessary to tell normal from abnormal.
- c. Look at the placement of the thumb. The distance from the phalangeal/metacarpal crease on the index finger to the point of thumb connection to the palm is about half the distance from the same crease to the crease between the palm and the wrist.

d. Look at length of the thumb by seeing how high up on the index finger the tip of the thumb reaches. The thumb has only two phalanges. The normal length thumb should come to a point between the metacarpal/phalangeal (MP) and proximal interphalangeal (PIP) crease of the index finger.

Figures



Abnormalities

a. Fingers

- 1) Polydactyly
- 2) Syndactyly
- 3) Camptodactyly
- 4) Abnormal shape – (tapered fingers, thin, tubular). Tapered fingers may indicate hypoplasia of the distal phalanges.
- 5) Short fingers – may be general or specific to a few fingers. The short fifth finger is a common dysmorphic feature and is a sign of growth retardation during development. The middle phalanx becomes triangular which leads to associated clinodactyly. When the phalanx is very small, there may be only a single interphalangeal crease. The tip of the fifth finger should reach the distal IP joint of the ring finger.

b. Thumbs

- 1) Short
- 2) Wide
- 3) Proximally placed thumb is abnormal
- 4) Finger like shape, sometimes due to a third phalanx

Normal variants

a. Normal hand structure is more standardized than foot structure, which is not surprising given the greater importance of the hand in development.

11. Nails

Significance & embryology

The finger nails begin to develop at 10 weeks, starting with a thickening of the epidermis. The size and shape of the nail reflect the size and shape of the distal phalanges. The nail is about two-thirds the width of the finger. The shape of the nail is slightly convex and slopes down to the proximal nail bed. Toe nail development lags 3-4 weeks behind the finger nails. Nails grow consistently at a slow rate throughout life, affected by medical conditions, age and even time of the year.

Examination techniques – simple inspection of the size and shape

Abnormalities

a. Size

- 1) Small nails are abnormal. If generalized it reflects hypoplasia of the distal phalanx. Often just one nail, especially the fifth nail is affected.

- 2) A large broad nail may indicate duplication of the distal phalanx.
- 3) Potter's thumb has a short wide nail and may affect the big toe nail.

b. Shape

- 1) Spoon shaped or concave nails are abnormal
- 2) Narrow, hyper convex nails reflect hypoplasia of the distal bony tuft of the phalanx.
- 3) Tapered nails usually become more convex distally.
- 4) A broad short thumb or big toe nail.
- 5) Dysplastic, distorted nails are abnormal. It may occur in one nail, especially the thumb and first finger or many. It may be a sign of fetal exposure to hydantoin.

Normal variants

a. Nails in infants may be quite small and have a concave or spoon shape.

b. Gray areas & pitfalls

Toe nails are generally more variable and anomalies are of less import than finger nails.

12. Feet Structure & Size

Significance & embryology

The development of the feet is analogous to the hands but lags by a few days. The axis of the foot is straight forward with no significant bending and when standing makes a 90° angle with the lower leg. The arch is lower in infants, but should never have a convex /rocker bottom shape.

Examination techniques

a. Size

- 1) Size can be judged either by inspection or direct measurement. To measure, hold the foot out and with a tape measure from the tip of the great toe to the back of the heel.

b. Shape/structure

- 1) With the person standing inspect for deviation at the metatarsal/phalangeal joint, either varus or valgus.
- 1) Inspection provides information on the shape and configuration of the feet including the axis of the foot, the shape of the arch and the prominence of the heel (calcaneus).
- 2) Inspection of the toes looks for polydactyly, clinodactyly, camptodactyly and very small toes.

Abnormalities

- a. Small (<3%) or large (>97%) are abnormal. Small feet are more likely to be significant and large feet mainly are familial with the exception of Sotos syndrome.
- b. Polydactyly.
- c. Syndactyly either cutaneous or osseous. (exception is mild syndactyly of the 2nd and 3rd toes).
- d. Irregularly placed toes
- e. Bulbous tips of the toes (tree toad toes).
- f. Short broad distal great toe.
- g. Hallux valgus, i.e. valgus position of the great toe.
- h. Clinodactyly which may lead to overriding toes.
- i. Hammer toes in young people. In older adults the extensor tendons may shorten to cause hammer toes.
- j. Club foot is the common name for a bent foot.

Normal variants

a. The second toe is longer than the great toe, called the “patrician” foot as opposed to the “plebian” toe where the length is graduated from the great toe to the little toe.

b. Syndactyly of the 2nd and 3rd toes with less than ~40% fusion.

Gray areas & pitfalls

a. Individuals with autism tend to have increased joint laxity. None of the signs of joint laxity, including flat feet (pes planus) distinguish ASD individuals who are dysmorphic from those who aren't.

b. Feet are more apt to be affected by intrauterine constraints than the hands. Thus, many foot deformities are deformations due to intrauterine positioning, muscle weakness or hypoplasia. Fixed and severe deformities such as a talipes equinovarus foot are due to malformations of the bones about 50% of the time.

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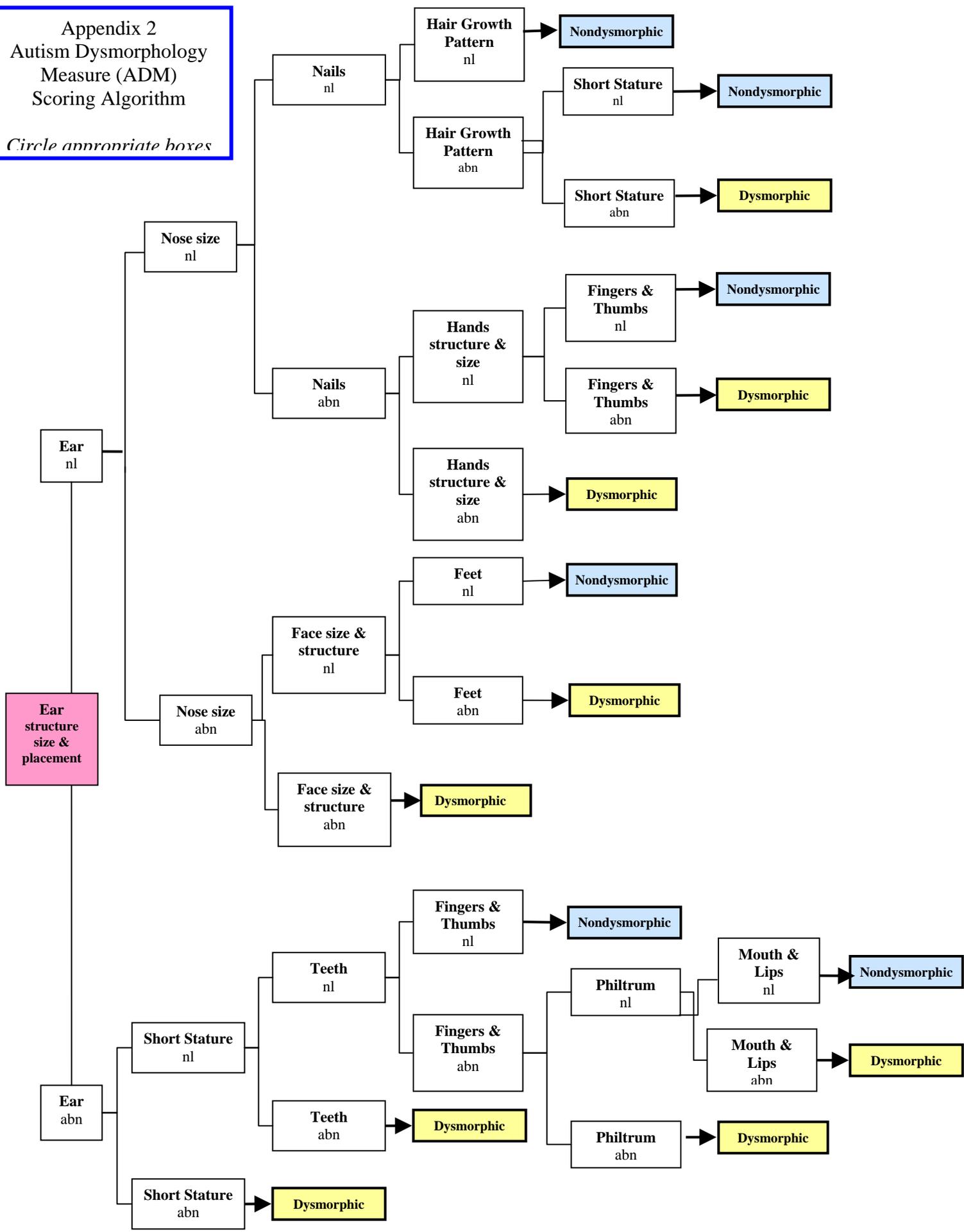
Rodier, PM, Bryson, SE, Welch JP (1997): Minor malformations and physical measurements in autism: data from Nova Scotia. *Teratology* 55:319-325.

Appendix 1. Autism Dysmorphology Measure Work Sheet

Name:		Birth Date: ____/____/____		Exam Date: ____/____/____		
Age: ____yr ____mo		Patient ID:		Examiner: Examiner code:		
Height ____ inches ____%		Weight ____ lbs ____%		OFC ____ cm ____% = occipital frontal circumference		
Ear length ____ cm ____%		Outer canthus ____ cm ____%		Inner canthus ____ cm ____%		
Hand length ____ cm ____%		Finger length ____ cm ____%		Foot length ____ cm ____%		
Body Areas & commonly observed dysmorphic features			Notes	NI/ Abn	In a Parent	Dysmorphic Yes/No
STATURE Short stature <10%						
HAIR GROWTH PATTERN						
Unusual hair whorl/pattern; Widow's peak; Frontal upsweep/ cowlick						
EAR STRUCTURE, SIZE, PLACEMENT						
EAR = Asymmetric; Dysplastic; Prominent or Protruding; Simple; Lop ear; Auricular pits/fistulas/tags HELIX = Over-folded; Notched; Crumpled; Pits on helix ANTIHELIX = Prominent. SIZE = Large, Small ears/microtia PLACE = Low-set, Posteriorly rotated						
NOSE SIZE Large/long; Small/short						
FACE SIZE & STRUCTURE						
SIZE = Small; Thin/long; Coarse features; STRUCTURE = Asymmetric; Flat; Triangular; Mid-face hypoplasia; Flat malar region; Prominent mandible/ prognathism; Small mandible/ micrognathia; Chin dimpled, grooved, pointed						
PHILTRUM						
Long; Short; Prominent/deep; Simple/flat; Wide						
MOUTH & LIPS						
MOUTH = Large/macrostomia; Small/microstomia; SHAPE = Cupid bow; Down-turned corners; Open mouth look LIPS = Cleft lip; Prominent upper lip; Thin upper lip; Prominent/everted lower lip; Thick lower lip						
TEETH						
Small; Wide spaced; Abn shape; Irregular/crowded; Enamel abn						
HANDS - Large hands, small hands						
FINGERS, THUMBS						
FINGERS = Clinodactyly; Camptodactyly; Short/hypoplastic metacarpals; Syndactyly; Tapering; Thin; Short; Long; Wide THUMBS = Broad, triphalangeal						
NAILS						
Short; Small/hypoplastic; Deep-set; Dystrophic, ridged; Hyperconvex/clubbed						
FEET						
FEET = Large; Small; Wide; Club; Varus TOES = Short; Syndactyly 2-3; Syndactyly not 2-3; Wide-spaced toes; Broad; Camptodactyly/hammer toes; Over-riding BIG TOE = Hallux valgus						
ADM Algorithm Score - Dysmorphic ____ / Non-dysmorphic ____ / Equivocal ____ (use rarely)						

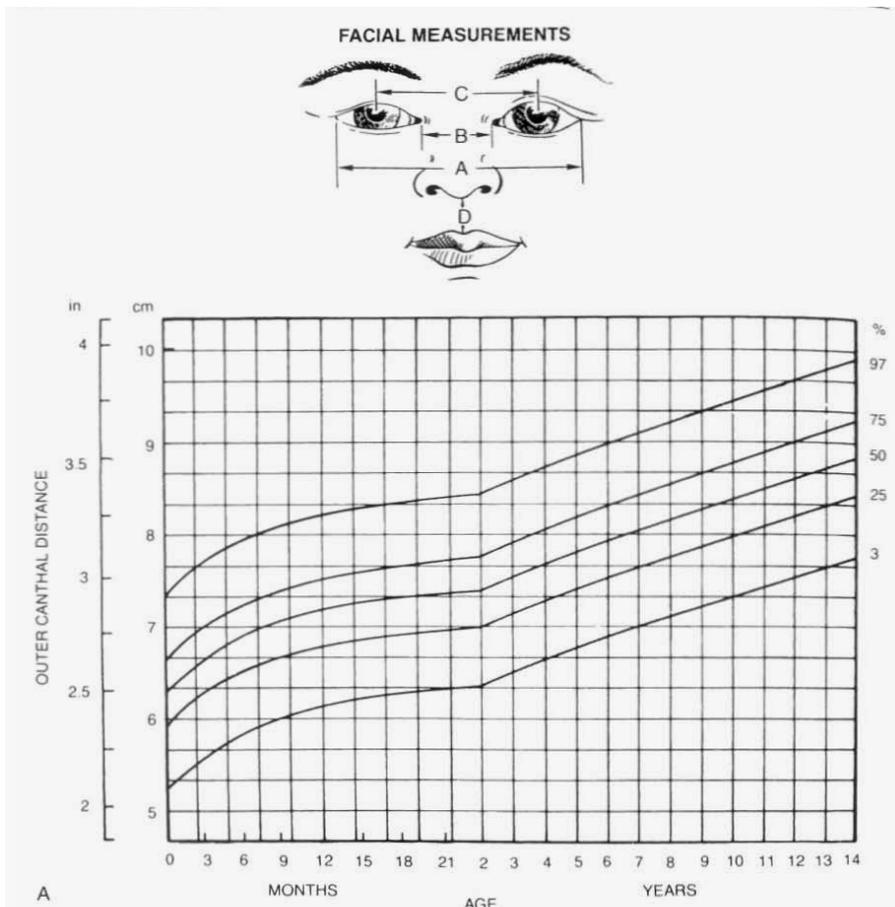
Appendix 2
Autism Dysmorphology
Measure (ADM)
Scoring Algorithm

Circle appropriate boxes



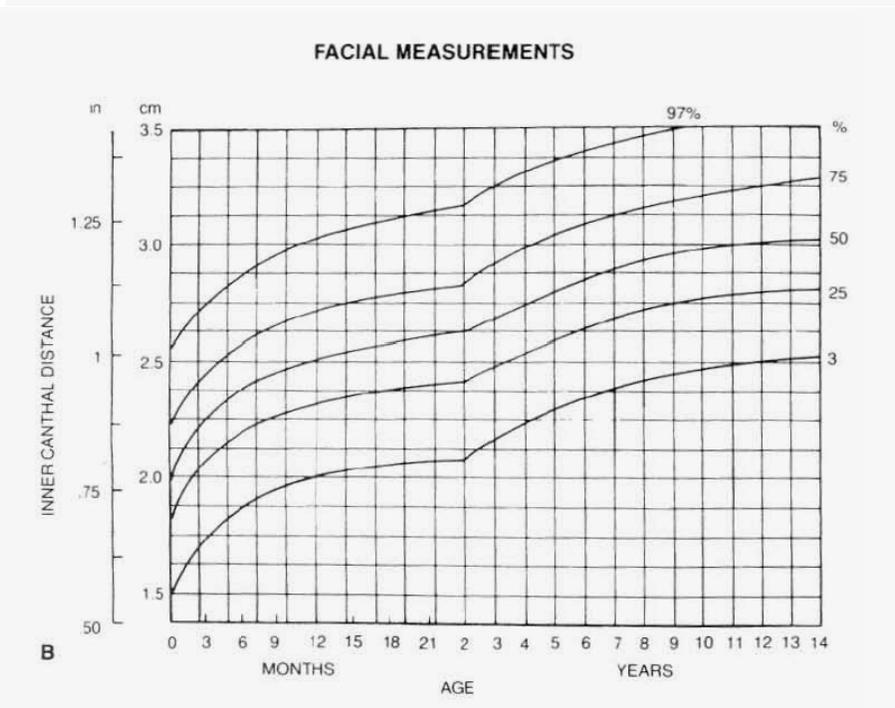
Appendix 3.

Normal Standards from Smith's Recognizable Patterns of Human Malformations

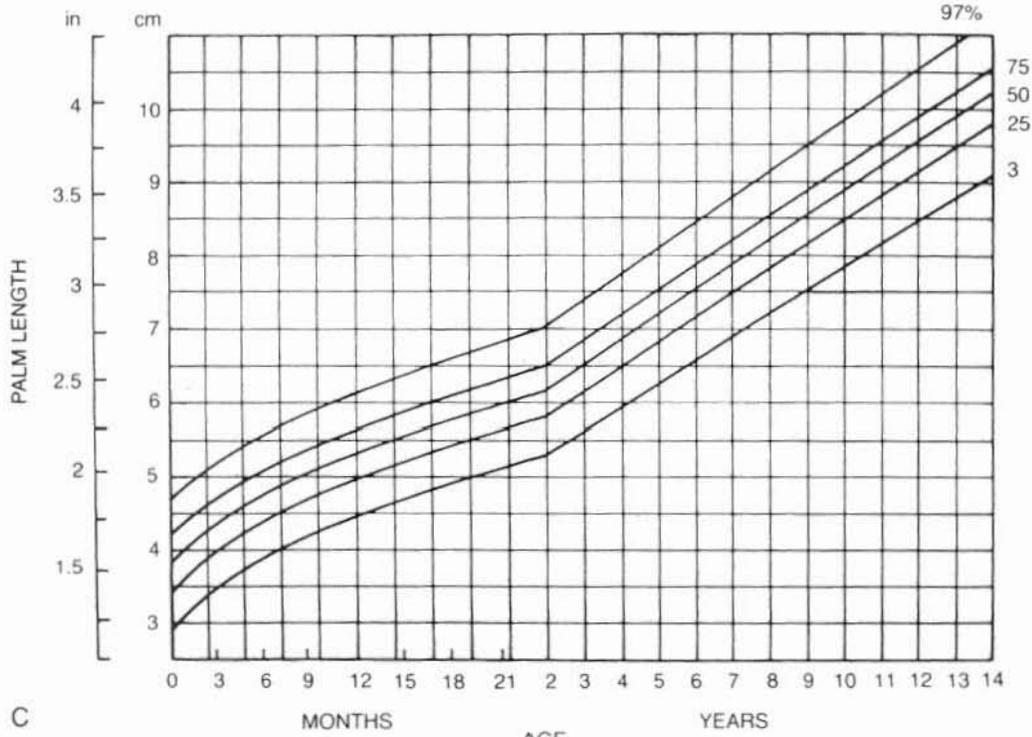


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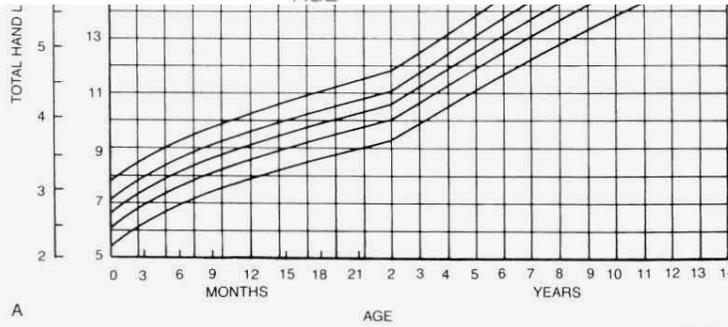
FIGURE 6-18. Outer canthal (A), inner canthal (B), and interpupillary (C) measurements. (From Feingold M, Bossert WH: Birth Defects 10(Suppl 13), 1974. With permission of the copyright holder, March of Dimes Birth Defects Foundation.)



HAND MEASUREMENTS



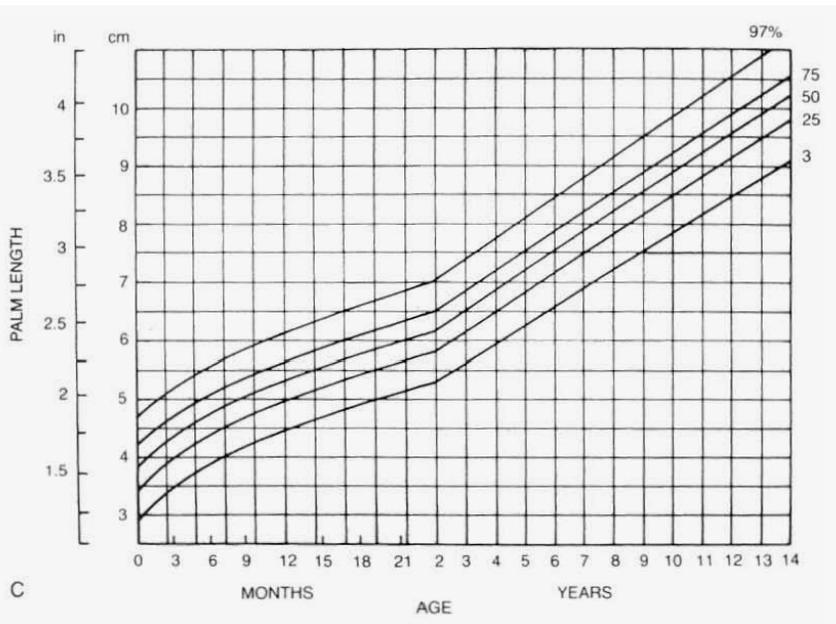
C



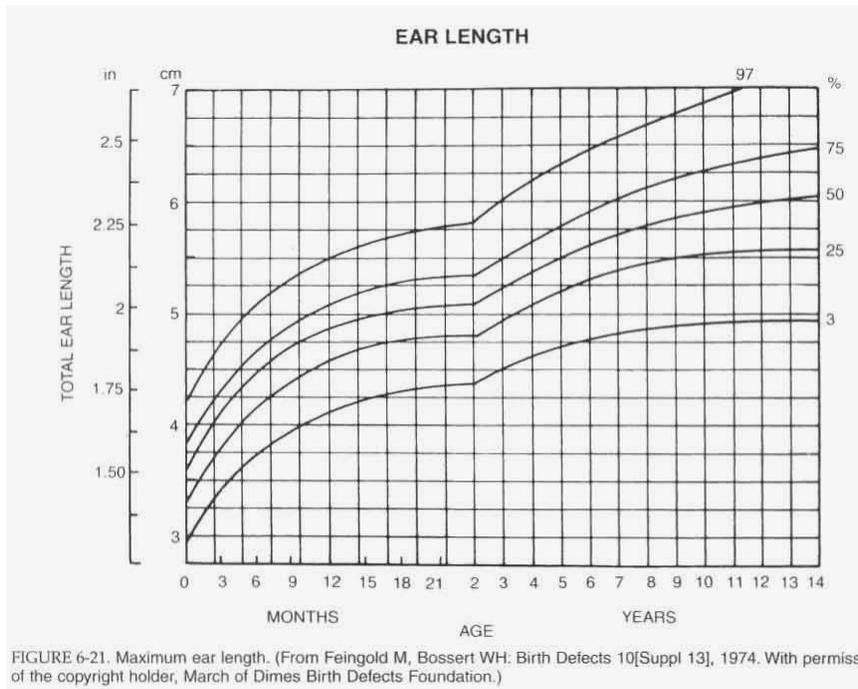
A

Continued

FIGURE 6-15. Hand length (A), middle finger length (B), and palm length (C). (From Feingold M, Bossert WH: Birth Defects 10[Suppl 13], 1974. With permission of the copyright holder, March of Dimes Birth Defects Foundation.)



C



Judith Miles, University of Missouri
 1-10-08 edition