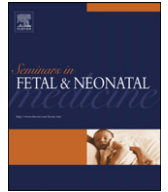




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A newborn with unusual morphology: some practical aspects

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S U M M A R Y

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Newborns with an unusual phenotype with or without malformations are common in the practice of every paediatrician. Determining whether the phenotype is a variation of normal or should be considered abnormal and, if the latter, also finding the cause can be extremely difficult. Here the main steps that should be followed in the diagnostic procedures are discussed. A careful family history and detailed physical examination remain the hallmarks of the investigations in all newborns. Very frequently clinical photographs will facilitate discussing patients with colleagues. Additional investigations usually include radiological examinations of all body parts that show abnormalities, and screening of the heart, kidneys, eyes and hearing. The studies with the highest yield are cytogenetic analyses which nowadays often involve microarray assays. In the near future, total exome sequencing will be available for diagnostic purposes which will have a major impact on the diagnostic process.

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1. Johnny

Julie and Geoff were devastated: the doctor had told them that their newborn Johnny looked a bit unusual and possibly had a heart problem. Surely, he was a bit small but during the pregnancy all controls had been perfect and Julie even stopped smoking when they decided to start their family! Fortunately they had heard from several friends that their paediatrician, Dr Childcare, was as her name suggests, and also very experienced. So they eagerly awaited her further investigations and conclusions.

So what would Dr Childcare do? The friends of Julie and Geoff were right: she was an excellent paediatrician, worked in a systematic way, and had a few simple principles she always followed. We will follow her steps.

2. Family history and physical exam

If Dr Childcare reads medical journals she would almost get the impression from the bombardment of papers describing sophisticated tools that this is authentic modern medicine. But she knows that is not true. A study of causes of mental retardation may illustrate this.¹ The authors studied 281 consecutive patients with mental retardation and were able to detect the cause in 53%. Subsequently they analysed what had been the tools that allowed

them to establish that diagnosis. It appeared that in one-third it had been just taking a careful history and physical examination, in another one-third it had been further studies directed by data from the same history-taking and physical examination, and only the last one-third was found by using a screening by all the sophisticated techniques described in literature (Fig. 1). Carefully taking a family history and performing a physical examination still remain the physician's most important tools.

In taking the history one should not just ask about consanguinity between the parents, miscarriages that the couple may have had, or malformations or syndromes in the family. It is increasingly understood that one should also take tumours into account.² This is based on the double function that many genes have: a gene may act as a developmental gene before birth but may function in a different way, including a function in growth regulation, after birth. A gene that is mutated and therefore leads to malformations before birth will still be mutated after birth and then can cause an increased chance for developing tumours. Indeed children with cancer were found to have a chance of 7.2% of having a syndrome.³ Such mutated genes can be inherited from either parent, which should also prompt detailed questions about cancer in the families.

3. Nomenclature

After a physical examination Dr Childcare will record the findings in the file. But how should she describe Johnny's nose? All too often two doctors describing the same nose will use different terms to do so. It seems trivial but it is not. If colleagues use different terms to describe the same feature there is the risk they will

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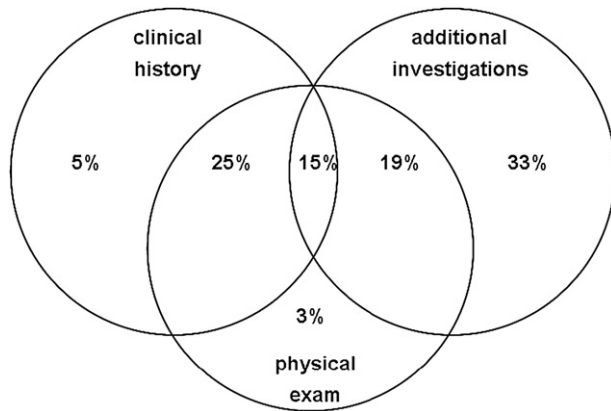


Figure 1. Percentages of three different investigations which were found to be essential in diagnosing children ($N=150$) with mental retardation and multiple congenital anomalies. If two circles overlap, two types investigation were essential; if all three overlap, all were essential. (Adapted from van Karnebeek et al.¹)

subsequently consider different entities that may be present, and it may cause unexpected severe problems that may even lead to the wrong management scheme. In children with uncommon signs or entities powerful search machines such as the London Dysmorphology DataBase and POSSUM are often needed to find all possible diagnoses. However, the use of wrong terms will yield a wrong list of possible diagnoses, and may lead to unneeded additional investigations (Box 1).

Box 1. An example of the consequences of a mistake in describing physical findings.

Searching the London Dysmorphology Data Base using a descriptor from physical examination yields possible diagnoses. If a newborn has an extra skinfold at the inner corner of the eye, it can be described as

- *telecanthus* which yields 129 hits
- or as
- *epicanthi* which yields 319 hits

The overlap between both is 36 hits.

→ Using a single different descriptor of a physical finding can direct an investigator in very different directions

In a recent series of papers terms used to describe the human phenotype including the complete face (Fig. 2) and the distal limbs were redefined.⁴ In the near future the remaining body areas will also be dealt with. The terms are already widely accepted and indeed form a basis for the ICD classification that is currently being developed (S. Aymé, personal communication).

4. Pictures

The importance of a standardized set of good quality clinical pictures of every child with unusual external signs or malformations cannot be overstated. Children with (possible) syndromic entities often have complex disorders, and need to be discussed with many colleagues from different specialties. Increasingly such discussions are not only conducted with colleagues within the same hospital but also with colleagues elsewhere: information technology allows us easily to contact top specialists for particular symptoms or disorders

anywhere in the world. Good illustrations of the total child, the face in two directions, hands and feet, and details from any body part that looks unusual, will facilitate such discussions greatly.

Pictures will also allow comparison of findings at different ages. There are many entities in which manifestations change with age, and recognition of such entities can depend on the changes.

Pictures may also serve a completely different goal, well known to Dr Childcare. The risk that newborn infants with malformations or a syndrome will die can be increased depending on the diagnosis. All too often parents hardly have the opportunity to see their child, especially the mothers after a caesarean section. In such situations pictures of a child can be a treasure for the families. The hospital of Dr Childcare has the policy to make pictures of all newborns that died, without all medical apparatus or plasters that cover a face, and in a friendly, clean cot with a toy of the family next to the child. No doubt this is one of the reasons why families think Dr Childcare fulfils her name.

5. Further clinical studies

A child that shows some unusual physical features may well have additional abnormalities. This has been studied by several investigators.^{5–8} All found a similar correlation: with an increasing number of minor anomalies the chance of finding a major anomaly increases significantly (Fig. 3). So it is also useful to search for other anomalies in such children. Finding additional malformations may also have an immediate consequence for patient care. The standard protocol of Dr Childcare includes a check for additional malformations of the heart (echocardiography), kidney (abdominal echography), eye (ophthalmological examination) and hearing (in newborns usually otoacoustic emissions or brainstem evoked potential). The brain would be another organ to check. However, transfontanel sonographies are useful for a general overview but insufficient for details, and computed tomography or magnetic resonance imaging will often need general anaesthesia. Therefore the more detailed neuroradiological studies are only performed if either the sonography showed signs of significant abnormalities, if there are neurological symptoms (which may include microcephaly or macrocephaly) that indicate an increased chance of brain malformations, or there are other findings of which co-occurrence with brain malformations is well known, such as hypotelorism or pigmentation abnormalities of the skin. In older children a marked developmental delay may be the reason to perform neuroradiology.

General radiological studies are often very informative. In general one should X-ray all body parts that show abnormalities. Frequently the radiological characteristics add just the extra data needed for the diagnosis. If several body parts such as a long bone and (part of the) spine already show abnormalities, one should consider that there is a more widespread dysostosis or skeletal dysplasia,⁹ and a full skeletal survey is indicated (X-skull; X-thoracolumbar spine in two directions; X-thorax; X-pelvis; X-arm [either left or right], X-hand [either left or right], and X-leg [either left or right]). The same series of X-rays is indicated in patients with (marked) growth retardation since that is also a strong indication for a skeletal dysplasia.

Other screenings for physical abnormalities should be performed, dictated by the findings of the initial physical examination. Short humeri will urge to check for a peroxisomal disorder; abnormal skin pigmentation may fit a chromosomal breakage syndrome; asymmetry may point to a chromosome mosaicism, etc. It will depend on the experience of Dr Childcare and other physicians in charge to recognize all these characteristics, or in case they have insufficient experience to ask a colleague from paediatrics or clinical genetics to help them to recognize these.

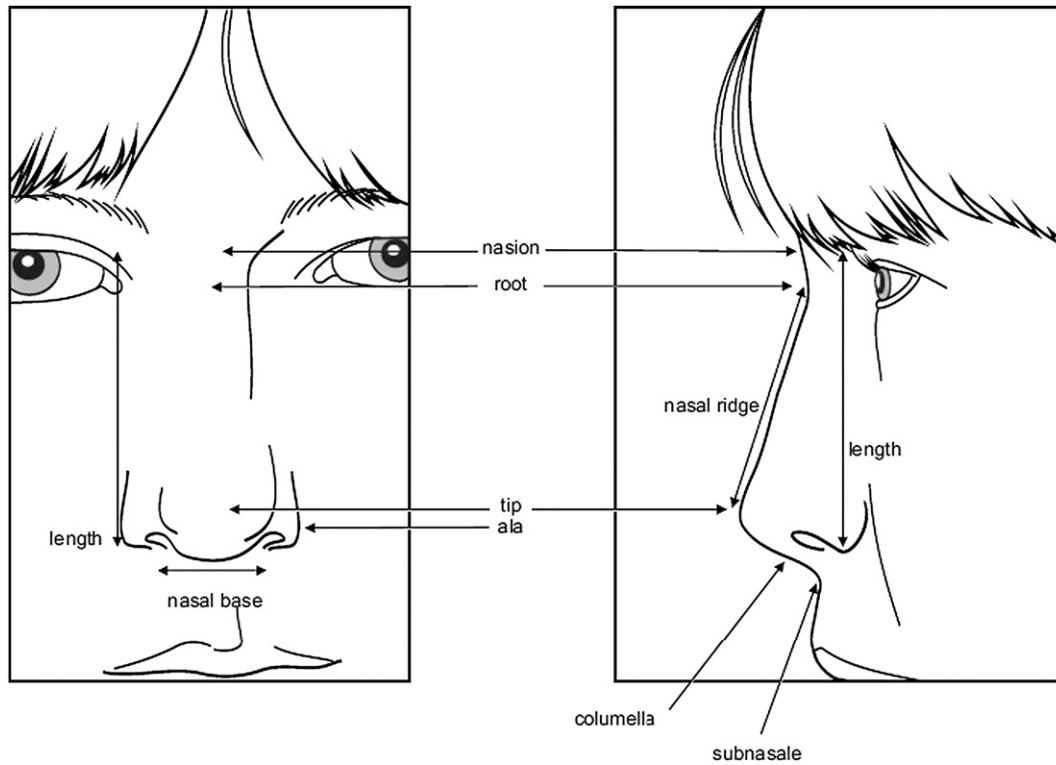


Figure 2. The nose as example of the anatomical descriptors according to the recent redefinitions of the human phenotype.⁴

6. Laboratory studies

The number and nature of possible additional laboratory studies is enormous. At present the studies are chosen based on the yield of abnormal results and the consequences for direct patient care either to the patient or to the family.

A search for chromosome imbalances is probably the test with the highest yield in fetuses or newborns with malformations. Percentages have ranged from 18%¹⁰ to 35%¹¹ if only classical cytogenetic methods are taken into account. In many northwestern European countries and the USA, microarrays have become the first-line technique in studying patients with malformations and/or developmental problems. With this technique deletions and duplications are detected, also very small ones such as the deletion of region 22q11, which is very commonly deleted in children with

cardiac defects (Fig. 4). Such microarray techniques add another 10% to the yield of chromosome analysis of malformed fetuses¹² and newborns.¹³ In many other countries classical cytogenetic studies are performed, to which fluorescent in-situ hybridization or multiplex ligation-dependent probe amplification studies are added if there is a clinical suspicion for a particular chromosome abnormality.

In the presence of mainly unusual facial characteristics many colleagues would add a metabolic screening of the urine in their total plan of investigation, but such studies have often been neglected in newborns with true malformations. Still, this is not justified. Smith–Lemli–Opitz syndrome is a well-known example of a metabolic disorder that goes along with not only unusual facial features but also many malformations such as an extra finger or complete sex reversal.¹⁴ The group of congenital disorders of glycosylation (CDGs) is rapidly expanding and is now known often to co-occur with birth defects.¹⁵ A recent unexpected finding has been a disturbance of the purine and pyrimidine metabolism in patients with Miller syndrome in whom the main symptoms are malar hypoplasia, coloboma of the lower eyelid, micrognathia, segmentation defects of the spine and loss of the fifth fingers and toes.¹⁶

The number of entities for which we know the causative gene is increasing rapidly, and samples can be acquired to search for mutations. However, this can only be done if one has an idea which entity a child might have and which gene might be involved. If there is no clue for a diagnosis one cannot search for mutations. At the present time this limits molecular analyses.

However, this will change in the near future. The techniques to check the whole genome for mutations are rapidly developing and may be available for diagnostics within five years. The first available technique will be total exome sequencing in which only those parts of our genome that code for proteins (exons) are investigated for the presence of mutations. The disadvantage is that not all

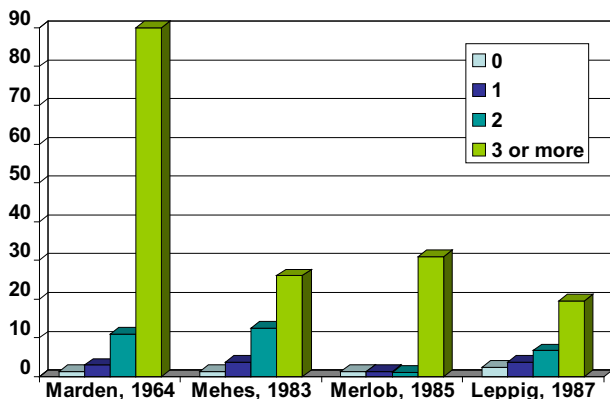


Figure 3. The likelihood of detecting a major malformation in children in whom zero, one, two, or more than two minor errors in morphogenesis were found.^{5–8}

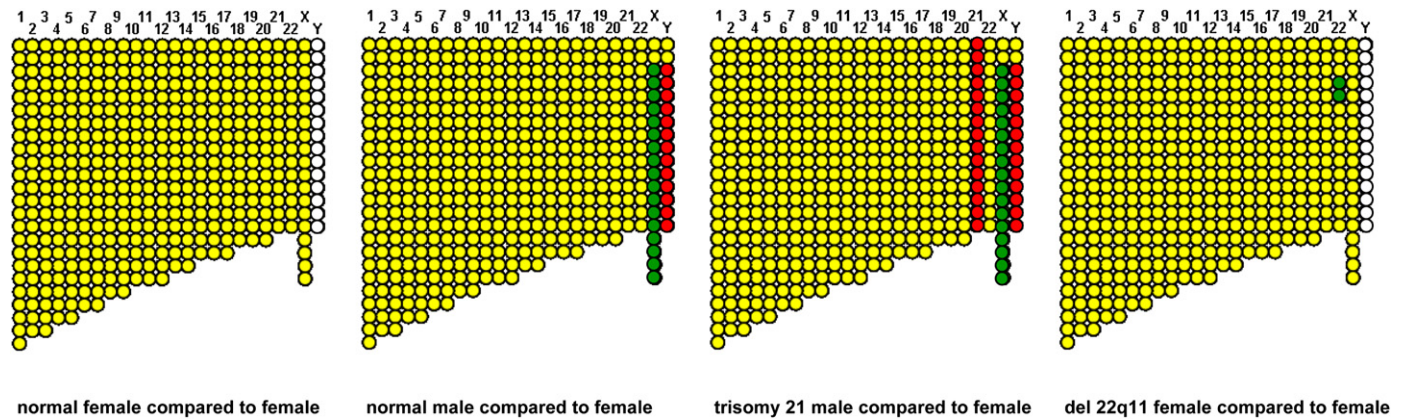


Figure 4. Principle of the mechanism of microarrays using comparative hybridisation. If for a particular chromosome region the amount of DNA of the studied patient and the reference DNA are the same, the circle is yellow. If more material is present in the studied patient the circle is red, and if less material is present the circle is green. The results in a patient with Down syndrome and del22q11 are shown as examples.

changes in exons are detected, and all changes outside the exons are missed. No doubt exome sequencing will be exchanged for total genome sequencing in the years thereafter, depending on the speed with which we will be able to deal with such huge amounts of data.

If either total exome or total genome sequencing has been shown to function well for a reasonable price it may supplant chromosome analysis, metabolic screening and directed molecular studies. This would have tremendous advantages, but would also require careful handling and storage of all data as well as continuation of respect for the privacy and autonomy of patients.

7. Diagnosis

In the end a diagnosis should be made. There are two major ways to find this. One way is to gather all information as mentioned above, and to search in textbooks such as the ‘Smith’¹⁷ or the ‘Gorlin’¹⁸ on the internet by putting major findings in PubMed or OMIM, or by using search machines such as the LDDB or POSSUM. It can be difficult to retrieve the right diagnosis if the manifestations in the child are unusual but a major sign or symptom is missing. The lists of possible diagnoses can be very long, and it may seem that the additional studies needed are endless. Sometimes one can recognize a particular combination of features in a child (‘pattern recognition’) known to co-occur in a particular group of disorders such as a chromosome anomaly or particular metabolic disturbance. This way of working closely resembles the other way by which a diagnosis can be made, namely ‘Gestalt diagnosis’. It means that one recognizes immediately the combination of findings in a child, without needing to describe all individual features. Surely this can only be done if one has unusually extensive experience in evaluating children with congenital anomalies. No matter which method is followed there is still a significant chance that the diagnosis cannot be made at that time, in which case careful long-term follow-up (‘watchful waiting’) is of extreme value. Children often change significantly with time, and frequently a diagnosis that had remained hidden at birth is immediately clear at one year of age. Time is on the patient’s and on our side.

Dr Childcare was a truly experienced paediatrician, which also meant she knew her limits, and that she needed to ask for help for a diagnosis in Johnny. She also realized very well that there would be the danger of making the wrong diagnosis in him. For parents undergoing a nerve-racking wait, the diagnosis often gives great relief. Information from the internet will be gathered, all ins and outs for further diagnostic and therapeutic management are established and the prognosis becomes fixed. If then, after a while,

it appears all this was wrong, since the diagnosis was wrong, it causes extreme worry and sometimes anger in families and the trust in the medical profession becomes severely hampered. It is much better to state that one does not know the diagnosis than to state the wrong diagnosis.

So Dr Childcare asked for help from one of her colleagues in clinical genetics, who was able to help her with the diagnosis and further management.

8. Johnny again

Johnny had a microcephaly, a small nose with depressed nasal bridge and upturned tip, and a smooth philtrum. He had mild prenatal growth retardation. The cardiologist diagnosed a muscular ventricular septum defect. Other basic studies failed to show other major malformations in Johnny, and chromosome analysis including a search for a deletion of region 22q11 gave a normal result. The family history eventually gave the clue to the diagnosis. Julie had a brother who was living in an institute for the mentally retarded but he was stated to have had a birth trauma and was unavailable for further studies. Julie herself had some problems at school but she had been able to get her certificates. She was known to the dermatologist because of a chronic non-specific dermatitis that did not respond to the various treatment schedules. The clinical geneticist combined the findings in Johnny with the dermatitis and mild learning problems in Julie, and checked her urine: indeed Julie had phenylketonuria (PKU)! In retrospect all findings in Johnny fitted very well with a maternal PKU syndrome.¹⁹ With many difficulties eventually Julie’s brother was tested, and he also was found to have PKU. All further planned studies in Johnny were cancelled, Julie and Geoff were informed and molecularly tested, and Julie was put on a diet as she was absolutely sure she would like to have more children, and she understood well that this way her own illness would not harm her babies anymore.

Dr Childcare guided them through this initially difficult period and was able to prevent Julie from blaming herself for the problems in Johnny. And Johnny himself? He showed that maternal PKU does not always lead to severe problems as his subsequent development was only mildly delayed.

Conflict of interest statement

None declared.

Funding sources

None.

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