Dysmorphology as a tool in detection of rare syndromes

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Introduction: Most of the dysmorphic syndromes belong to a group of rare disorders. Some of the described syndromes are extremely rare and, therefore, difficult to diagnose. Cytogenetic and molecular tools for their detection are expensive and frequently unavailable so far. Thus the only chance to establish the diagnosis is clinical recognition in most of them. Dysmorphology is one of the latest established medical sciences, derived from several others - clinical genetics, pediatrics and embryology. As a starting point of evaluation in clinical genetics,, dysmorphology deals with discovering and interpreting patterns of human development and its variants.
Materials and methods: We present patients with various rare syndromes from our practise. Most of them don't have easily accessed diagnosis. General methods in dysmorphology are used, detecting non-random combinations of major and minor anomalies. The definitions from International centre for birth defects for malformative features were used. Algorithm of procedures including suspicion, inspection, physical examination and establishing hypotheses has been followed in order to confirm the proper diagnosis of the syndrome.
Discussion: The diagnosis of a specific dysmorphic syndrome is state of the art for clinical recognition, which includes gathering, sorting and combining the set of minor and major anomalies in recognizable pattern. Major anomalies which are crucial for patient's health have second-degree significance compared to minor anomalies. Although not life-threatening, minor anomalies and their combination have major role in detecting rare syndromes. Specificity and sensitivity of some minor anomalies will be discussed.
Conclusions: Distributing information about patients with rare syndromes on international level is important in gathering similar patients in order to establish their molecular background. Dysmorphological approach for such patients is the first step towards this goal.

Rare diseases are diseases which have low prevalence - according to the European Commission for rare diseases - 5 per 10 000 in general population. They are highly debilitating diseases which handicap someone's health and quality of life. It has been estimated that 6% to 8% of the population in Europe is affected by one of this diseases (1). About 80% of rare diseases have genetic background. The need for their distinguishing from other common diseases emerges from several things. First, the need for rising up the attention for these diseases comes from the lack of knowledge of general practitioners to recognize them as soon as possible. Second, we are approaching the era for creating orphan drugs to some of them; therefore starting therapy earlier is essential for patient's health. And finally, information of larger cohort of patients and variability within one disease, gives an opportunity for research strategies worldwide.

Dysmorpic syndromes are usually enlisted in the databases for rare disorders. They include non-random combinations of variable disorders, more or less affecting the health of the patient. Although they don't have adequate treatment jet, there is a need to recognize them in purpose to get a better knowledge of a particular syndrome and study its variability in population as well as between populations. This gives rise to evaluate and establish possible pathogenetic and molecular mechanisms.

Some of the syndromes described in the literature and databases are extremely rare. Those syndromes are difficult to diagnose since most of the clinical geneticists are not able to see most of them in their working lifetime. Therefore many tools and databases are established to make the syndrome easily recognizable (2). Accurate dysmorphic evaluaton of every patient is one of this tools, which is prior to other medical and laboratory investigations. Dysmorphic assessment leads the diagnostic procedure in exact direction and is cost effective. Disorders that dysmorphologists are investigating are not limited by the age group, organ system or sex.

Dysmorphology is a part of clinical genetics which investigates and interprets forms of human form including all structural defects - hidden or surface. The term "dysmorphlogy" has been coined in 1960 by Smith which comes out from Greek words - dys (disorder) and morph (form). As stated, dysmorphology is science of abnormal forms in the human. A substantial part of its investigation is identification and classification of anomalies and their combinations. It relies on the knowledge of several sciences- genetics, pediatrics and embryology.

Figure 1: Disproportionally short stature of the figure of goddess Bess suggests for achondroplasia

Such diagnostic procedure is, mostly dependent on careful inspection of affected individuals. Therefore dysmorphology is visual specialty, which predisposes knowledge of a large numbers of syndromes described in articles and databases, as well as ability to recognize and combine features and variables in the human appearance. The skill to be a meticulous observer is becoming sharper with time, when sense of size, proportion and symmetry of facial and body structures is developing (Hall).

Clinical recognition of rare syndromes

Dysmorphic syndromes contain non-random combinations of different disorders that can be major - that influence a lot the patient's health, and minor - that don't have a great impact of his health (Donnai). The art of clinical recognition demands knowledge, recognition, collecting and sorting various minor and major anomalies in a recognizable patern. The phrase: What you see is what you get defines told by the comediat Phlip Wilson, dfines the process of recognizing the syndrome disorders (Aarskog).

The biggest problem in recognizing the dysmorphing syndromes are their rare appearance , variability, as well as development of some features later in life and disappearance of the others. Incomplete presentation as well as variable expressivity are obstacles in proper distinguishing, too. For example, the same mutation of FGFR can be present in the parent with high forehead and its offspring with full-blown picture of craniosynostosis.

The process for establishing the diagnosis follows the main principles in medicine in general, following the rules for logical connection and critical evaluation of gathered data. The diagnosis in dysmorphology can be solved immediately, when the dysmorphologyst have already seen such a problem, or by integrative approach searching for other features or consulting the literature.

Materials and methods:

We present patients with various rare syndromes from our practise. Most of them don't have easily accessed diagnosis.

General methods in dysmorphology are used, detecting non-random combinations of major and minor anomalies. The definitions from International centre for birth defects for malformative features were used.

Algorithm of procedures including suspicion, inspection, physical examination and establishing hypotheses has been followed in order to confirm the proper diagnosis of the syndrome.

Results:

Every dysmorphic syndrome has been separately evaluated, including proportions of the face, body and extremities, as well as major and minor anomalies. Major anomalies were not the main determinants of a particular syndrome. According to the existence, for example of major cardiac anomaly, the examiner couldn't determine the syndrome only by this fact. Minor anomalies can point to a specific syndrome.

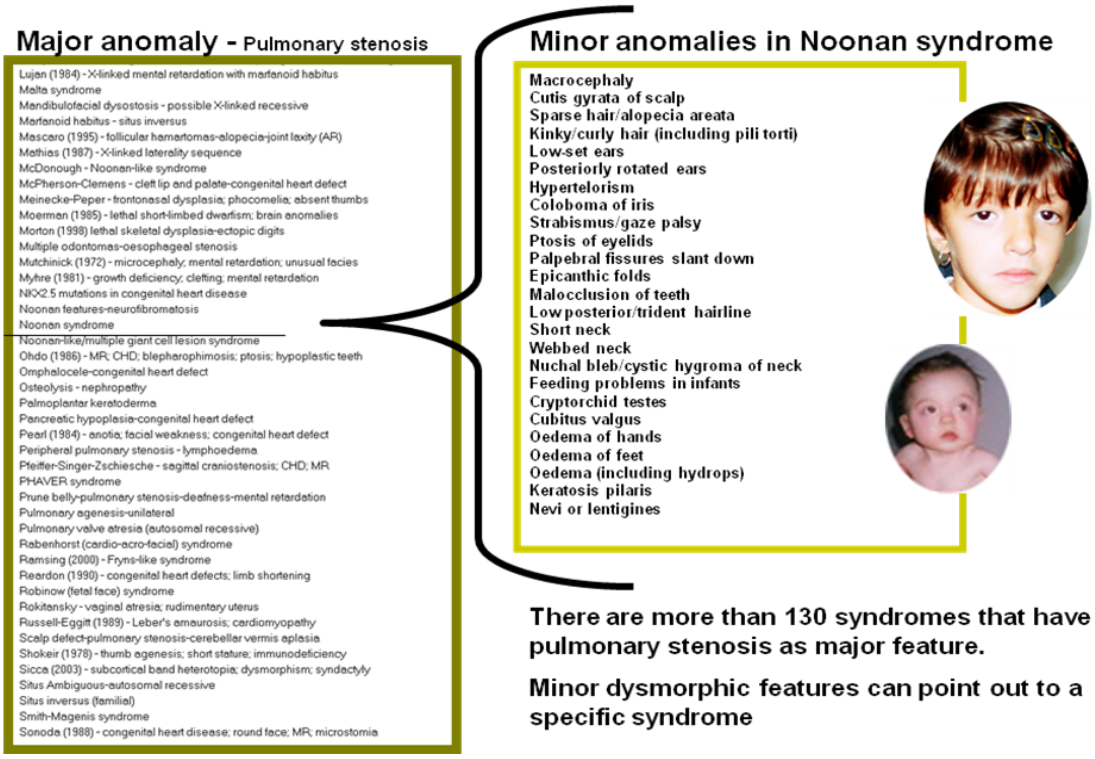

Figure 2: The value of major and minor anomalies in establishing the diagnosis

Unspecific features such as epicantus, clinodactily, wide-set eyes are far more common in many syndromes and, therefore not many useful in distinguishing syndromes. Consequently, variable combinations of several dysmorphic features should be used and different hypotheses should be given till the proper diagnosis appear. In such cases minimal "cluster" of features in necessary.

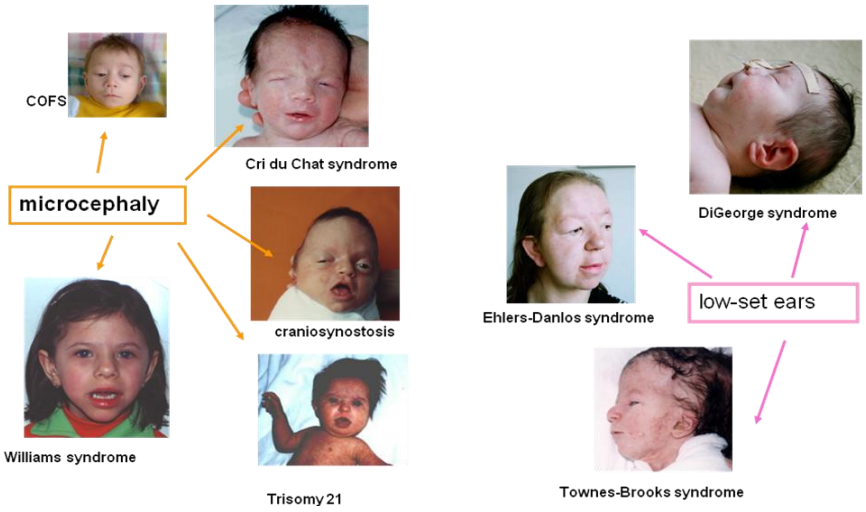

Figure 3: Common features in distinguishing syndromes are not useful

Specificity - frequency in appearance, and sensitivity in detecting the specific syndrome (proportion of patients of a particular syndrome that have a certain feature) is most reliable fact that can lead the diagnosis in proper direction. So, many unnecessary investigations could be avoided only by detecting such features.

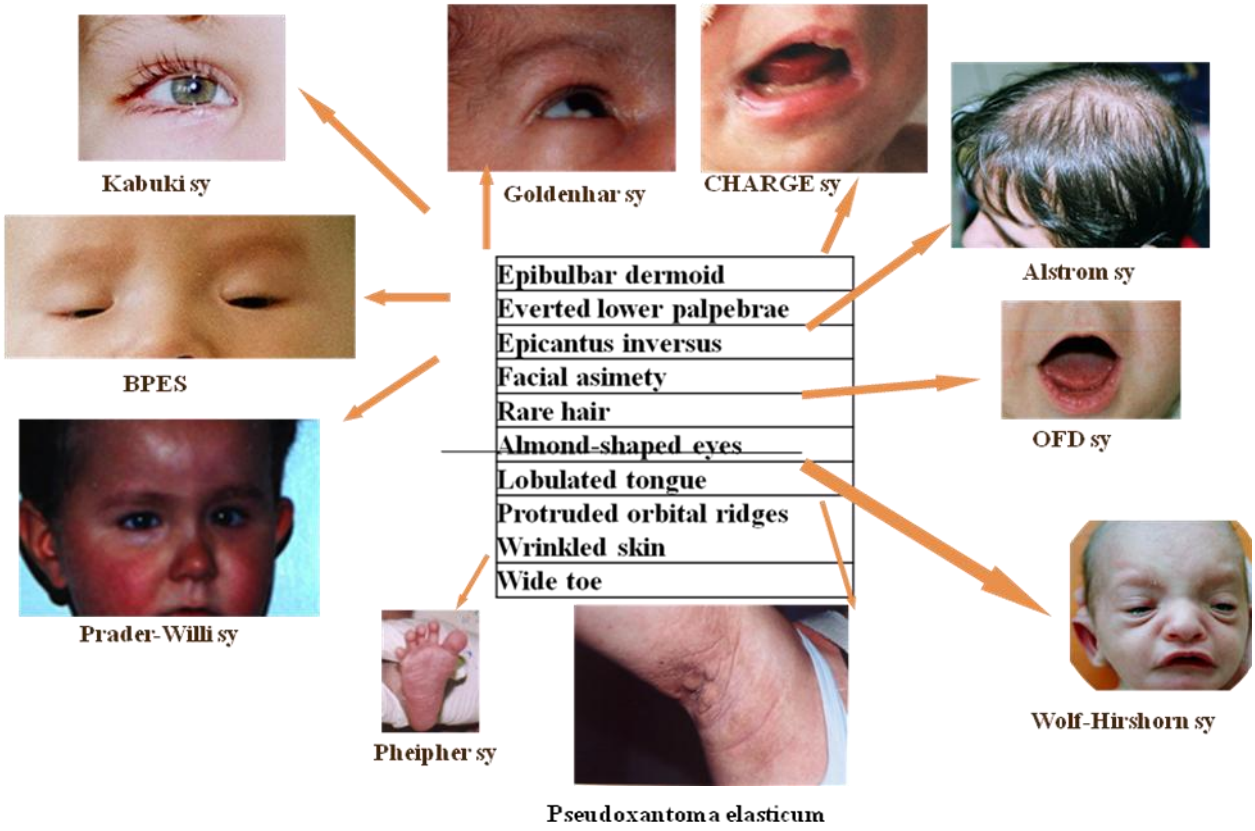

Figure 4: Specificity and sensitivity of some features are strong proof for a particular syndrome

Discussion and conclusions

The boundary that distinguishes normal from abnormal form of the facial and body structures is not defined precisely. Most of the evaluation relies on subjective decision of the examiner. Frequently, in the dysmorphological vocabulary there are descriptions such as small face; long nose, short philtrum. The question stays -how short, how long. Quantification of dysmorphogenesis is possible with the precise computerized anthropometric measurements, as well as with the evaluation of minor and major dysmorphic features. After the Human Genome Project, a new project was established- Human Phenome Project - with the only purpose - to describe human variations better.

The diagnosis of a specific dysmorphic syndrome is state of the art for clinical recognition, which includes gathering, sorting and combining the set of minor and major anomalies in recognizable pattern. The process of defining he syndrome can have three

solutions - having a proper solution; inability to find the right answer, and existence of a new, not jet published syndrome. It is not necessary to rule out the diagnosis if not all of the features are not described. However, having a discordant features which are not part of a particular syndrome rules out the diagnosis. Sometimes it is better the patient not to have a diagnosis than to have a wrong one.

Major anomalies which are crucial for patient's health have second-degree significance compared to minor anomalies.

Although not life-threatening, minor anomalies and their combination have major role in detecting rare syndromes. Specificity and sensitivity of some minor anomalies are crucial for establishing the proper diagnosis.

Most of the rare dysmorphic syndromes don't have appropriate treatment so far.

However, distributing information about patients with rare syndromes on international level is important in gathering similar patients in order to establish their molecular background. Dysmorphologic approach for such patients is the first step towards this goal.

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