Syndrome Diagnosis: An adventure into the creative world of nature.

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Why write about syndrome diagnosis in genodermatology?

Patients with a skin manifestation as part of a syndrome deserve the benefit of all our wisdom and experience to get their diagnosis. We need one to develop cures for their afflictions in the future, but also to care for them and so lighten their burden as much as possible in the here and now. As scientists, we have to realize that the immense diversity of the "experiments of Nature" is instructive about normal biology and offers lessons that cannot be taught in another way. Thus, patients with inherited disorders deserve our attention for more than one reason.

Syndrome diagnosis is still more of an art than a science. While it is possible to formally discuss some important considerations, which we will do here, there is no substitute yet for practice. A lot of clinical exposure under the tutelage of an experienced clinician and much looking at clinical photographs in good books (see below) will usually get the interested clinician started. After that, hard work will bring the required expertise.

What is a "genodermatosis"?

Happle has defined a genodermatosis as a cutaneous phenotype caused by a single genetic aberration that may be a point mutation, a deletion or other chromosome aberration. This definition excludes all phenotypes that are caused by the action of more then one gene such as psoriasis and atopic dermatitis. Thus, it is perhaps too limited. After all, the chance of developing atopic dermatitis is heavily influenced by a single gene locus, *FLGN*[1].

Epidemiology of genodermatoses.

Most are rare disorders. The most frequent ones are neurofibromatosis (1:3000) and

tuberous sclerosis complex (1: 10,000).

Classification

The nosology of genodermatoses presents a major problem. Clinical classification schemes are by definition arbitrary. Ideally, disease categories would reflect biological reality and at the same time have clinical meaning, helping us to counsel and treat our patients. However, the clinical and biological heterogeneity of inherited skin diseases defies attempts at simple classification. For example, Küster et al in 2000 proposed a scheme based on the most prominent clinical characteristics[2]:

1. Disorders of cornification
2. The epidermolyses
3. Connective tissue disorders
4. Ectodermal dysplasias
5. Hair- and nail diseases
6. Pigmentary disturbances
7. Metabolic disorders
8. Genodermatoses characterized by benign tumors
9. Genodermatoses characterized by malignant tumors
10. Other

It will be immediately obvious that the scheme is just as arbitrary as any other. As an example, Küster et al group Cockayne syndrome under "Other". We know that it is a disorder of DNA repair that on the molecular level is a form of Xeroderma Pigmentosum, which in the above scheme is in group 9. Until we more completely understand human biology, an integrated classification that covers both phenotype and genotype characteristics in a meaningful way will remain elusive.

What is a syndrome?

The word "syndrome" is Greek for "walking together". A syndrome is formally defined as a group of symptoms that collectively indicate or characterize a disease, psychological disorder, or other abnormal condition. It is implicitly understood in the context of inherited disorders that the presenting symptoms have a single cause, which may or may not be genetic. Note that the definition is phenotypic, not pathogenetic.

Why is it important to recognize a syndrome?

There are many reasons why a doctor should be interested in syndrome diagnosis. The most immediately obvious one is that a diagnosis enables us to council and, increasingly often, treat our patients. Victor McKusick, one of the founding fathers of modern genetics, gives us even more reasons[3]:

1. Rare disorders can teach us much about the normal or about more common disorders.
2. Rare manifestations are sometimes valuable clues to the existence of grave internal disease.
3. People have them.
4. They are a break in the routine and "keep the physician's powers of observation from undergoing atrophy".

We feel that the third reason alone should be enough for any doctor.

When do we need to consider a syndrome?

When our patients present with multiple (skin) symptoms we should always consider the possibility that the symptoms have a common cause. Nature doesn't like coincidences. Always ask yourself "What is the chance that these symptoms should occur together, at this time and in this person?". Don't ignore symptoms, but follow these steps:

What to do when suspecting a genetic syndrome?

Step 1

Get the phenotype right and know what's important

The most important lesson here is to not ignore symptoms and abnormalities and always make sure that you have diagnosed them correctly. Don't be complacent. Remain critical of yourself. For example: an adolescent is referred with "acne" in the face that did not respond to standard treatment. Physical examination shows skin-coloured and papules around the nose and a patch on the lower back that looks like a collagenoma. Additional history taking reveals that the patient has had some episodes of epilepsy. Further examinations including abdominal CT then reveal bilateral kidney masses consistent with angiomyolipoma. A biopsy

of the perinasal lesions reveals an angiofibroma. Subsequent mutation analysis confirms the diagnosis of tuberous sclerosis complex. Hair follicle tumors sometimes mimic acne but do not respond to treatment.

Also, look further than the skin. Many syndromes cause recognizable facial phenotypes. Direct Gestalt recognition of these will not be a realistic goal for most of us, but we all can see whether a face conforms to the norm. If it doesn't, we will feel that it is "syndromic". This intuition is an important clue that should not be ignored. At the same time, the doctor should be aware that many people have minor anomalies, small defects of morphogenesis that are in themselves of little importance. Knowing what is a major anomaly and what is not is an essential part of syndrome diagnosis and much of the art centers around being able to define what the essentials of a particular phenotype are. Here, too, practice makes perfect.

Step 2

Nature does not like coincidences

If many symptoms and signs collide in a patient one should always consider prior probabilities. While so-called "collision syndromes" do exist, there is an inverse correlation between the number of anomalies that one person has and the prior probability of those anomalies having collided as a matter of chance. If those signs and symptoms then occur in regions or structures (including organs) that have a developmental and/or functional relationship, the level of suspicion should be raised further. For certain genodermatoses, one should look out for signs of cutaneous mosaicism. If skin lesions follow Blaschko's lines, one should very strongly consider the presence of a genetic anomaly that may be in the germ line. Finally, never forget to ask about family. Family history can make or break a diagnosis and tell you whether a patient may have a collision syndrome. For example, a young boy presents with nail dysplasia, hypodontia, dry skin, hypotrichosis and facial abnormalities consisting mainly of midface hypoplasia with a broad, flat nasal ridge. In addition, he has osteopetrosis and overwhelming bacterial infections. Ectodermal development, bone remodeling and immunity are related, both processes depend on NFkB signalling. The boy's skin and facial phenotypes are consistent with a form of ectodermal dysplasia. Combined with the other symptoms one then arrives at the diagnosis of OLEDAID (osteopetrosis, lymphedema, ectodermal dysplasia and immunodeficiency), which is caused

by NEMO mutations[4]. The mother will likely be a carrier and have incontinentia pigmenti Bloch-Sulzberger.

Step 3

Search and be creative

Before starting a search in the literature or in databases it is important to think thoroughly about the keywords to use. Unfortunately, terminology is hardly uniform and synonyms, metonyms and heteronyms abound. Thus, when searching with a certain combination of symptoms, it may be worth to generalize some. For example, go from "acne" to "skin". Realize that much of the genetics literature was not written by dermatologists and that some specialist terms may not be used that often and that some symptoms may not be considered important by non-dermatologists. As an example, try using the term "excoriation" to search the Online Mendelian Inheritance in Man (OMIM) database for the diagnosis of a patient with an itching scaling skin condition and spasticity.

A search may appropriately be made in books and both online and offline databases.

1. Books

At the moment the best tool to diagnose a syndrome or genodermatosis[5] are the clinical guides of genetic skin disorders. In most of the modern clinical guides the text takes a user-friendly approach to present difficult topics more clearly and to make them easier to learn.

- Caputo R, Tadini G. Atlas of genodermatoses, London, New York: Taylor & Francis, 2006. ISBN10: 1-84184-251-6; ISBN13: 9-78-1-84184-251-6
- Spitz JL. Genodermatoses. A clinical guide to genetic skin disorders, Philiadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Lippincott Williams & Wilkins, 2005. Second edition. ISBN 0-7817-40886. If you can buy only one book for your clinic, buy this one.
- Gorlin RJ, Cohen MM, Hennekam RC. Syndromes of the head an neck. Oxford, New York: Oxford University Press, 2001. Fourth edition. ISBN 0-19-511861-8. Has a very good chapter about skin and about minor criteria. Highly recommended.
- Jones, Kenneth Lyons. Smith's recognizable patterns of human malformation. Philadelphia, Pennsylvania: Elsevier Saunders, 2006. ISBN 0-7216-0615-6. Contains

good symptoms tables with differential diagnosis and an extensive chapter describing minor anomalies. The standard work.

2. Online databases

- OMIM at http://www.ncbi.nlm.nih.gov/omim

  Online Mendelian Inheritance in Man (OMIM) is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.

  This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). .

- LDDB

  This database contains the Winter-Baraitser Dysmorphology Database, The Baraitser-Winter Neurogenetics Database and The London Ophthalmic Genetics Database. The late Robin Winter was Professor of Clinical Dysmorphology and Clinical Genetics at the Institute of Child Health, London and Dr Michael Baraitser was formerly Consultant in Clinical Genetics, at Great Ormond Street Children's Hospital, London. Both authors have written about syndrome recognition and gene identification. Although not specific for dermatology, this database is interesting and useful because of the vast amount of information it covers and its approach to syndrome delineation, focusing on key phenotypic features. Standalone database, requires a license.

- POSSUM/OSSUM

  POSSUM (Pictures of Standardised Syndromes and Undiagnosed Malformations) and **OSSUM** (Illustrated **Database** of Skeletal Dysplasias), Database c/o Murdoch Institute, Royal Columbian Hospital, Parkville Victoria, Australia 3052. Not as popular as the LDDB but very good, emphasizes key features in a slightly different way but in essence comparable. Is available via the Internet after a license has been bought.

- PubMed

  PubMed Central (PMC) is the U.S. National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature.

Step 4

The diagnosis, or ask the expert

Having done all of the above, you will either have a diagnosis or an idea of which category your patient's disorder belongs to. Perhaps in contrast to many other disciplines, making a syndrome diagnosis is rarely done alone. Discuss your patient with colleagues, known experts and in expert groups, such as the Dutch Task Force on Genodermatology. If you have the opportunity, consider starting or participating in a multi-disciplinary outpatient clinic together with clinical geneticists and/or pediatricians.

Step 5

Lab testing

Diagnostic laboratories.

The genetic cause of many syndromes and genodermatoses is now known. Several genes can be analyzed in DNA diagnostic labs. Centres in The Netherlands are listed in www.erfelijkheid.nl/centrakg.php and their tests in www.dnadiagnostiek.nl/zoekenStart_nl.php. For genes associated with very rare disorders that are not in this list, contact the department of Dermatology of the Maastricht University Medical Center. They can test about 100 genes.

Step 6

Counseling and support groups

If needed, refer the patient (and his/her family) to a clinical geneticist for appropriate counselling.

Patient and their families might need support groups. As these might be rare diseases these might be available in the Netherlands via www.erfelijkheid.nl/zoek/zoeklotgenoten.php.

Step 7

Prenatal diagnosis

Making a correct diagnosis of rare hereditary skin disorders is of utmost importance for genetic counselling. For some disorders, prenatal diagnosis may be indicated. Increasingly, mutation analysis is taking the place of morphological analysis. Indications for prenatal diagnosis or even pre-implantation diagnosis should be discussed with a clinical geneticist.
Patient information is available at www.zwangernu.nl

Step 8

Therapy

The ultimate therapy would be one that corrects the causal defect. We still have a long way to go but for some disorders there are now some treatments available that actively ameliorate symptoms. Glivec for neurofibromatosis I is one example, Anakinra for Muckle-Wells syndrome another. Most inherited skin disorders can only be managed symptomatically. This task should be taken seriously. It may be frustrating to know that your patient will have his or her condition for life, but that doesn't mean that adequate supporting therapy cannot be given.

References

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