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PERSPECTIVE **ANESTHESIA & CONCURRENT DISEASE**

Anesthetic management of rare diseases - OrphanAnesthesia Project

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*"Rare diseases are **rare, but** rare disease patients are **numerous**"*

Today we have thousands of rare diseases described and as there is only sparse information available on the management of most of them and much less on anesthetic management, the OrphanAnesthesia Project (https://www.orphananesthesia.eu) gathers the available information, merging evidence from the literature with the experience of specialists in the subject to better benefit all physicians involved in the perioperative care of the patients with these diseases. A disease is called "rare" when it affects only a small number of individuals. Obviously, this definition may vary between regions and over time. In Europe, a disease is considered to be rare when it affects a maximum of 5 out of 10,000 people. The project was founded on the initiative of the DGAI Scientific Working Group on Pediatric Anesthesia (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V.) working jointly with the European Society for Pediatric Anesthesiology (ESPA) and the European rare disease portal Orphanet. Initially, the idea of an open access database with information about anesthesia in patients with rare diseases emerged, which was implemented in 2011 with the project's web platform. Since then, doctors dedicated to the topic, from all over the world, have actively participated in the main objective of the OrphanAnesthesia Project, which is the publication of recommendations for the safe anesthetic management of these patients.

Orphanet (www.orpha.net) is a French working group from the French National Institute for Health and Medical Research (INSERM) in Paris. Orphanet was established by the INSERM in 1997. This initiative became a European endeavor from 2000, supported by grants from the European Commission. Orphanet has gradually grown to a Consortium of 40 countries, within Europe and across the globe. It provides information on rare diseases, including: patient organizations, scientific research projects and referral centers.

It maintains large database on the internet;

1. The Orphanet Rare Disease Ontology (ORDO): It was jointly developed by Orphanet and the European Bioinformatics Institute (EMBL-EBI) to provide a structured vocabulary for rare diseases, capturing and describing the available information about the relationships between diseases, genes and other relevant features, forming a useful resource for the computational analysis of rare diseases.

2. The HPO – ORDO Ontological Module (HOOM): It qualifies the annotations between a clinical entity (from ORDO) and phenotypic abnormalities from HPO (Human Phenotype Ontology) according to the frequency and by integrating the notion of diagnostic criterion.

3. Rare Diseases & Classifications:

Orphanet maintains the Orphanet nomenclature of rare diseases, essential in improving the visibility of rare diseases in health and research information systems: each disease in Orphanet is attributed a unique and stable identifier, the ORPHA code. The nomenclature

is organized in a poly-hierarchial classification, and data set includes: types of disorders, flags of disorders, new relations between disorders, and characterization of the alignments between disorders and external terminologies or resources (OMIM, ICD-10, MeSH, UMLS, MedDRA and GARD). The alignments are characterized in order to indicate if the terms are perfectly equivalent (exact mapping) or not. For analysis purposes, each disorder is attributed to a preferred classification by linking it to the head of classification entity (Linearization of disorders). As some decisions could be made somewhat arbitrarily, we have written a set of rules to make sure attributions are consistent (see below procedure on Linearization rules for Orphanet classifications). Hence, users are allowed to access to 4 different data sets: Orphanet nomenclature files for coding, Rare diseases and cross referencing, Classifications of rare diseases and Linearization of disorders.

4. Epidemiological Data:

Orphanet curates data concerning the epidemiology of rare diseases. Orphanet carries out a systematic survey of literature in order to estimate the prevalence and incidence of rare diseases.

The rare diseases epidemiology dataset includes the preferred name and ORPHAcode of the diseases, groups of or subtypes, and their point prevalence, birth prevalence, lifelong prevalence and incidence, or the number of families reported together with their respective intervals per geographical area.

The rare diseases natural history dataset includes the preferred name and ORPHAcode of the diseases, their type of inheritance, interval average age of onset and age of death.

5. Rare Diseases & Functional Consequences:

In this dataset, a table with diseases listed in Orphanet annotated with functional consequences or environmental factors leading to limitation of activity or restriction of participation. It allows the scientists in different countries to copy the files and run their own country datasets.

The Orphanet portal also contributes to the dissemination of new recommendations for the OrphanAnesthesia Project.

As of 2014, the recommendations began to be published in the German magazine “Anästhesiologie & Intensivmedizin” (https://www.ai-online.info/supplements-orphananesthesia.html), and in this way, they can be cited for the academic purposes.

Each recommendation is presented in a standard format and undergoes a review by at least one anesthesiologist and another specialist in the disease. OrphanAnesthesia is an international project and today has approximately 200 recommendations originally published in English, with approximately 500,000 downloads. As an example, on December 11, 2020, the recommendation on anesthesia in a patient with Tetralogy of Fallot, accounted for 13,121 downloads of its file. Translations into German, Spanish, Portuguese, Czech, Italian and other languages are being produced.

All colleagues are welcome to contribute to the project. Information can be obtained on the platform. Contribution can be made by preparing a recommendation for review, offering to review or translate an existing recommendation into your language. A rare disease that needs a recommendation can also be suggested.

Internet Resources

1. OrphanAnesthesia http://www.orphananesthesia.eu
2. Orphanet https://www.orpha.net/consor/cgi-bin/index.php
3.Orphadata Ontologies http://www.orphadata.org/cgi-bin/index.php#ontologies
4. Orphadata http://www.orphadata.org/cgi-bin/rare_free.html
5. OMIM® - Online Mendelian Inheritance in Man® http://www.omim.org
6. GARD https://rarediseases.info.nih.gov
7. Syndrome & Maladies rares en Pediatrie http://tinyurl.com/m-rares