

Genetic Aspects of Uncommon Diseases

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Key Points

- Hereditary diseases represent 80 % of the rare diseases
- Hereditary diseases are the consequence of the pathological modification of one or a few genes
- The diagnosis, which may be done before birth, is confirmed by the identification of one or more mutations
- The knowledgebase “Orphanet” (<http://www.orpha.net/>) is the reference website for updated informations on genetic and rare diseases.

Genetic diseases are those that are caused by the alteration of a gene. They represent 80 % of so-called “rare diseases” (whose prevalence is less than one case for 2,000 persons), or approximately 6,000 pathologies. Interestingly, the prevalence of adult respiratory distress syndrome is estimated at 30/100,000. It shows that the notion of disease rarity is relative when it comes to intensive care medicine! Genetic diseases affect 1–2 % of births in the world, or approximately 10 million people in Europe. People suffering from genetic diseases are therefore alone and isolated but, at the same time, they represent a large population. That explains why these diseases are a real public health priority. Fortunately, not all genetic diseases lead to intensive care unit. Aggressive medical management in the intensive care unit is not always the only available solution and should in most cases be considered in light of a multidisciplinary team and ethical approach.

Rare or orphan diseases have been acknowledged since the beginning of the 1980s. The United States provided a first definition in the Orphan Drug Act that

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passed in 1983: “Any disease affecting less than 200,000 people”, which at the time was equivalent to a prevalence of 7.5/10,000 in the United States. The prevalence threshold is 4/10,000 in Japan. In France, it is 5/10,000. Various plans to provide medical care for rare diseases have emerged in France. In 1992, a fast-tracked procedure was implemented to allow orphan diseases drugs to be granted marketing authorisation. In 1995, a commission for orphan drugs was established and in 1997, *Orphanet*, a portal on rare diseases and orphan drugs, was set-up. More recently, the National Plan on Rare Diseases (2005–2008) was launched to “ensure equity in the access to diagnosis, treatment and provision of care”. The plan led to the creation of centres of reference on rare diseases. To give a few examples, in France, about 15,000 people suffer from sickle cell disease, 8,000 from amyotrophic lateral sclerosis, 6,000 from cystic fibrosis, 5,000 from Duchenne muscular dystrophy, 500 from leukodystrophy, while only a few cases of progeria are reported. 65 % of rare diseases in France are serious and debilitating; they have an early onset (appearing before the age of 2 in two cases out of five); they cause chronic pain in one patient out of five; they lead to the occurrence of a motor, sensory or intellectual deficit in half of the cases, and to a disability or loss of autonomy in one case out of three. Overall, rare diseases are life-threatening in half of the cases.

Physiopathology of Genetic Diseases

Genetic diseases result from a pathological change in one or several gene(s). Among these are distinguished:

- Hereditary genetic diseases, transmitted to the offspring via the reproductive cells, namely gametes.
- Multifactorial diseases, the majority of which are caused by multiple factors: environment, lifestyle and type of food consumption, biological and genetic factors. This is the case for cancers, for some types of cardiovascular diseases, for neurodegenerative diseases, and for infectious diseases. The respective roles played by the various factors in these diseases is highly variable. And so is the degree of incidence of the mutated genes.

Among genetic diseases, a distinction can be made between those caused by the mutation of a single gene and those resulting from the “accumulation” of multiple genetic abnormalities. The first ones are called “monogenic” or “Mendelian” since their transmission pattern follows the laws discovered by Mendel. The genetic diseases whose transmission is not Mendelian involve several genes, as well as non-genetic factors. This is the case of mitochondrial diseases (mitochondria are elements present in the cells, intended to generate the necessary energy for the cells), where the mutation affects the mitochondrial genome. Their transmission is particular as only women can pass them on and because the

mutated-gene expression is often mosaic. It is also the case of chromosomal diseases linked to the absence of a chromosome or to its presence in excess (such as Trisomy 21), or to abnormalities of the chromosome structure itself. Genetic diseases are also classified according to the organs and physiological functions they affect.

Finally, the penetrance of the disease is extremely variable, even within a family, which often complicates diagnosis and prenatal counselling.

Diagnosis and Treatments

Today, a gene mutation associated with a multifactorial disease can be identified through genetic testing.

However, given the many genes involved in these diseases, these tests do not so much provide information to foresee the evolution of these pathologies, as they provide information on the existence of a risk factor in a family's genetic makeup. However, the main benefit of genetic testing is to help formulate a diagnosis for patients showing clinical signs. Erroneous clinical diagnoses can therefore be definitely ruled out and those at risk can be screened.

Prenatal diagnosis is a genetic test performed on a fetus. It is a rare procedure, only intended for parents who may transmit a severe, incurable hereditary disease to their child. A prenatal diagnosis is proposed to families at risk following a specialized consultation. In addition to providing information and assessing the risk of a genetic disease, this consultation also allows the parents to benefit from a suitable psychological support.

The acknowledgement of rare diseases being recent, the development of specific treatments has only been prioritised by public authorities in the last 20 years. For the majority of the diseases, there is still no hope for a cure. Gene therapy is a very promising perspective.

The principle of gene therapy is simple: the genome of a cell is corrected by replacing a defaulting gene with its functional copy into the cell. Through this technique, it is therefore possible to correct a defective function or to compensate for a missing function in the target cell. The first significant success of this method was obtained in 2000 by the team of Dr. Marina Cavazzana-Calvo and Pr Alain Fischer, who succeeded in curing young children suffering from rare severe combined immunodeficiency (SCID), through the introduction of a gene-drug in their bone marrow cells.

Cell therapies use specific cells, administered to prevent, cure or mitigate a disease. Some of them have already proven their worth: transfusion of red blood cells and platelets to treat some types of blood diseases; skin graft for victims of severe burns; transplantation of stem cells that can produce massive populations of different cells and regenerate a damaged tissue; transplantation of insulin-producing cells (the islets of Langerhans) to treat insulin-dependent diabetes; transfer of dendritic cells which induce and regulate an immune response when the

Table 1 Genetic diseases that may be seen in ICU and whose prevalence is estimated between 5 and 50/100,000

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Tetralogy of fallot	45	Spo./AD	Neo./Inf.	Survival >85 % after ttt	Heart (peri-operative, or initial heart failure)	Surgery
Arrhythmic right ventricular dysplasia	44	AD/AR	Ad.	Normal risk = sudden death	Heart (sudden death, or heart failure at advanced stages)	Drugs, implantable cardioverter-defibrillator++
Elliptocytosis	35	AD	Variable	Normal (only 5–20 % have a severe disease)	Severe anemia, POC	Folic acid, transfusion, splenectomy
Osteochondritis dissecans	35	AD	Ad./Ad.	Normal	POC	Physiotherapy, Surgery
Malignant hyperthermia	33	AD	Variable	Mortality <5 %	Rhabdomyolysis	Dantrolene
Marfan syndrome	30	AD	Childhood	Depends on cardiovascular complications	Cardio-vascular	Multidisciplinary
Congenital hypothyroidism	29	AR	Neo./Inf.	Normal if early detection	Coma, ...	Substitutive ootherapy
Alpha-1-antitrypsin deficiency	25	AR	Variable	Linked to the pulmonary and hepatic dysfunction	Liver (cirrhosis) lung (emphysema)	Alpha-1 antitrypsin (IV) ongoing clinical trials, lung/liver transplant
Long QT syndrome	25	AD/AR	Childhood	Normal risk = sudden death	Heart (sudden death)	Beta-blockers, cardiac sympathetic neurolysis
Atresia of the small intestine	20	Spo./AR	Neo./Inf.	Depends on the length of the small intestine	POC	Implantable cardioverter-defibrillator
Isolated scaphocephaly	20	Spo./AD	Neo./Inf.	Normal	POC	Surgery
Hereditary spherocytosis	20	AD/AR	Variable	Normal if newborn bilirubin-encephalopathy is avoided	Severe anemia in neonates	Transfusion ± EPO Splénectomie

(continued)

Table 1 (continued)

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Agenesis of the corpus callosum—neuropathy	19	AR	Neo./Inf.	Depends on mental status	Epilepsy	Symptomatic/palliative
Dilated cardiomyopathy, familial	17.5	RX/ AD/ AR/ MH	Variable	Slightly reduced (risk of sudden death)	Heart (sudden death, or heart failure at advanced stages)	Drugs, implantable cardioverter-defibrillator ++
Bilateral renal agenesis	17	AD	Neo./Inf.	Death in utero, or near birth	–	Symptomatic/palliative
MELAS syndrome	16	MH	Childhood	Variable but prognosis is severe	Cerebral (seizures), Lung (myopathy), heart (heart failure)	Ongoing clinical trials
Disease of the maple syrup	15.6	AR	Neo./Inf.	Acute form: death in the first weeks of life if undiagnosed	Cerebral (coma, encephalopathy)	Hemodiafiltration, some rare forms are cured by thiamine administration
Deficiency of acyl-CoA dehydrogenase medium chain fatty acids	15	AR	Neo./Inf.	Normal if diagnosed	Severe hypoglycemia	Glucose (massive amounts)
Von Willebrand disease	12.5	AD/AR	Variable	Normal	Cerebral (hemorrhagic stroke), hemorrhagic shock (peroperative, delivery, ...)	Depends on subtypes, von Willebrand factor, desmopressine
Supravalvular aortic stenosis	12.5	AD	Variable	Variable but almost normal	Heart (Infarction, heart failure, sudden death), hypercalcemia, POC	Surgery
Cystic fibrosis	12	AR	Neo./Inf.	~35–40 years	Lung (failure), liver (cirrhosis)	Symptomatic/palliative

(continued)

Table 1 (continued)

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Sickle cell disease	11	AR	Variable	Unpredictable	Lung (thoracic syndrome), cerebral (Stroke)	Transfusion, hydroxyurea in severe forms
Prader-Willi syndrome	10.7	Chr 15	Neo./Inf.	Reduced (30–40 years)	Lung (chronic failure), heart (heart failure)	Substitutive opotherapy GH), special diet
Nephroblastoma	10.1	AD	Childhood	Survival >90 % with treatment	POC	Chemotherapy + surgery
Congenital adrenal hyperplasia	10	AR	Neo./Inf.	Good	Acute metabolic events (hyponatremia, hyperkalemia, acidosis; severe hypoglycemia)	Substitutive opotherapy
Isolated plagiocephaly	10	Spo./AD	Neo./Inf.	Normal	Intra cranial hypertension, POC	Surgery
Catecholaminergic polymorphic ventricular tachycardia	10	AD/AR	Childhood	Without treatment, sudden death before 20. Risk is reduced by treatment	Heart (sudden death)	Beta-blockers
Abnormal mitochondrial oxidative phosphorylation (nuclear DNA)	9	AR/MH	Variable	Reduced, but depends on the age of onset	Lung (chronic failure), heart (heart failure)	Symptomatic/palliative
Tuberous sclerosis	8.8	AD	Childhood	Normal with the exception of uncontrolled seizures	Cerebral (seizures), lung (failure)	Depends on localisation of tumors
Pierre Robin syndrome isolated (isolated Pierre Robin sequence)	8.8	Spo./AR	Neo./Inf.	Normal if diagnosed early	Lung (obstructive disease)	Surgery
Duodenal atresia	8.6	Spo./AD	Neo./Inf.	Normal	Neonatal ICU and POC	Surgery

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Table 1 (continued)

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Acute hepatic porphyria	8	AD/AR	Variable	May be normal. Depends on the frequency and severity of seizures	Neurological (Guillain-Barré), liver	Hemine (IV) carbone hydrates, liver transplant
Hemophilia	7.7	RX	Neo./Inf.	Normal	Hemorrhagic shock, POC	Transfusion of the missing factor Surgery, glucose
Beckwith-Wiedemann syndrome	7.3	AD/MF	Neo./Inf.	–	POC (omphalitis), Severe hypoglycemia	Surgery, glucose
Dystrophy	7	AD	Childhood	Normal	Lung failure	Physiotherapy, mechanical ventilation
Facioscapulohumeral						
Fryns syndrome	7	AR	Neo./Inf.	About 10–20 % in neonatal period	Lung (hypoplasia (diaphragmatic hernia), heart (malformations), Neuro	Surgery, but mainly palliative
Holoprosencephaly	7	AD	Neo./Inf.	High heterogeneity, so variable. Severe forms die in neonatal period	Lung (apnea), heart (rhythmic disease), cerebral (seizures), metabolic (diabetes insipidus)	Symptomatic/palliative
Sotos	7	AD	Neo./Inf.	Normal	Heart (malformations), cerebral (seizures), hypoglycemia	Symptomatic/palliative
Galactosemia	6.6	AR	Neo./Inf.	Normal if diagnosed early	Liver failure, septic shock	Galactose-free diet
Autosomal recessive polycystic kidney disease	6.5	AR	Childhood	Normal	Kidney (chronic failure)	Dialysis, transplantation
Amyotrophic lateral sclerosis	6	Spo./AD/AR	Adult	60–65 years	Lung (failure)	Symptomatic/palliative

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Table 1 (continued)

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Treacher-Collins syndrome	6	AD	Neo./Inf.	Variable: adults with few symptoms and severe forms with neonatal death	Lung failure	Surgery, symptomatique
Wilson disease	5.8	AR	Childhood	Normal	Liver (acute hepatitis, cirrhosis)	D-penicillamine, Triethylenetetramine
X-linked adrenoleukodystrophy	5	RX	Variable	Variable	Adrenal deficiency	Substitutive opotherapy, genetic therapy currently evaluated
Ciliary dyskinesia	5	AD/AR	Neo./Inf.	Slightly reduced is lung disease is well treated	Lung (obstructive disease), heart (malformations)	Symptomatique, Kine respiratoire, transplantation pulmonaire dans de rares cas
Duchenne muscular dystrophy and Becker	5	RX	Childhood	Duchenne : 30–40 years Becker: sub-normal	Lung (restrictive disease), heart (chronic heart failure)	Symptomatic/palliative
Hereditary fructose intolerance	5	AR	Neo./Inf.	Normal if diagnosed early	Acute liver failure and hemorrhagic shock if massive amounts of fructose are ingested	Fructose, sorbitol and saccharose free diet

Heredity: *Spo.* sporadic, *AD* autosomic dominant, *AR* autosomic recessive, *X* recessive linked to X, *MH* mitochondrial heredity, *MF* multifactorial. Onset age: *Neo.* neonatal, *Inf.* infancy, *Ado.* adolescence, *Ad.* adult, *POC* post operative care

immune system no longer recognizes, and therefore no longer rejects, foreign tumor cells; transfer of a certain type of liver cells, hepatocytes, which present a selective advantage to repopulate and rebuild a damaged liver.

Protein replacement therapy consists in replacing a defective protein by a recombinant protein. For example, in the case of Gaucher's disease, characterized by a deficiency in glucocerebrosidase, an enzyme whose recombinant form has been developed and used to replace the missing enzyme.

Finally, one should also mention the classic approach based on drug administration, which for example has been explored in the treatment of hereditary tyrosinemia, a liver disease occurring in children under the age of one, which results from the accumulation of metabolites causing oxidative damages to the cell. The treatment of this disease is nowadays improved by the administration of an inhibitor of the tyrosine metabolism.

Genetic Disease and Intensive Care

Given the large number of genetic disorders which can lead to intensive care admission, we have opted to present in a table the Mendelian genetic diseases whose prevalence range from 5 to 50/100,000 (in comparison, the prevalence of pulmonary fibrosis is 7/100,000, that of familial forms of Parkinson's disease is 15/100,000 and that of lupus is 50/100,000). All the information presented in the table is drawn from the *Orphanet* website (<http://www.orpha.net/>), a world reference in the field of rare diseases. It has a good search engine, and for each pathology it provides links to additional articles in French or English. Because the diseases mentioned in this work are very rare, the information presented here is likely to be obsolete by the time you read it. Therefore, it is advised to check the *Orphanet* website, which is regularly updated. One can also find on that website a document listing the centres of reference that are approved to provide medical care for a specific rare disease or a group of rare diseases. (http://www.orpha.net/orphacom/cahiers/docs/FR/Liste_des_centres_de_reference_labellises.pdf) This information is essential in order to obtain expert advice and whenever possible, to transfer the patients to these centres of reference (Table 1).