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THE PARLIAMENTARY OFFICE FOR SCIENTIFIC AND TECHNOLOGICAL ASSESSMENT

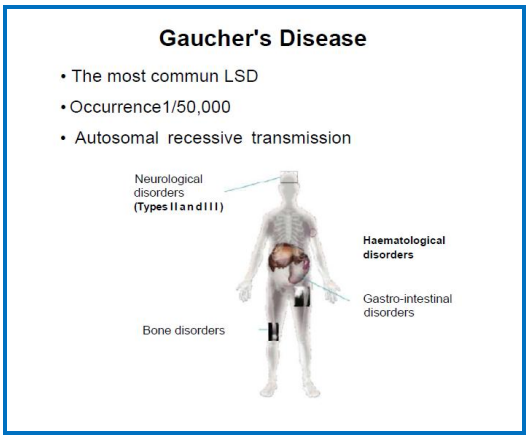
Monogenic Diseases: Current Issues

Public hearing organized by
Mr. Claude Birraux M.P. and Mr. Jean-Louis Touraine M.P.

The Parliamentary Office for Scientific and Technological Assessment (OPECST) was requested by the Standing Committee for Social Affairs of the French National Assembly to carry out a study carried out on drepanocytosis ("sickle-cell disease"). The OPECST decided to broaden this referral to the whole family of monogenic diseases. Thus a public hearing open to the press, entitled, "Monogenic Diseases: Current Issues", was organized on June 7, 2011 by Claude Birraux M.P. Chairman of the OPECST and Jean-Louis Touraine, M.P. It gathered researchers from a variety of fields as well as the delegates of associations representing sufferers. Its aim was to examine both the scientific and medical aspects of such diseases as well as various societal and legal issues linked to them.

This cross-disciplinary approach was absolutely essential given that monogenic diseases can develop from childhood and not only concern the sufferer or potential sufferer, but also his/her circle and in particular his/her family. The latter may be faced with numerous difficulties linked to providing support and care for the patient as well with the risks of stigmatization connected to the genetic origins of the disease.

The public hearing demonstrated that the scale of this phenomenon was significant, that it required substantial research in various fields and that it raised ethical and legal questions.



Common Diseases and Public Health Issues

Even though certain of these monogenic diseases are in themselves rare, their very number means that overall, when they are counted in all their forms, they occur as frequently as cancer and concern tens of thousands of people. They thus raise a substantial public health issue.

Drepanocytosis, which was at the origin of the referral, is the most widespread genetic illness in France. Today there are over 5,000 sufferers and these numbers could increase to 20,000 by 2020. Beyond the financial burden on our health system, the quality of life of the sufferers is significantly reduced. Many essential forms of treatment are not covered by national health insurance.

Genetic mutation of Drepanocytosis

The social integration of both patients suffering from this disease and of their circle, in terms of education and employment is difficult. This is particularly the case for mothers who must constantly provide treatment for child sufferers. Drepanocytosis sufferers feel they are discriminated against.

Data made available in a Florida *Medicaid* file indicate that in 2009, the average cost of treatment for a drepanocytosis patient in the United States came to around $2000 per month. The average annual cost for children was more than $10,000 and reached nearly $35,000 for older patients. The

Assemblée nationale - 101, rue de l'Université - Bât F. - 75355 Paris 07 SP - Tel: 01 40 63 70 65 - Fax: 01 40 63 70 95
Sénat - 15 rue de Vaugirard 75291 Paris Cedex 06 - Tel: 01 42 34 25 58 - Fax : 01 42 34 46 04
www.assemblee-nationale.fr - www.senat.fr

overall cost, for an average life expectancy of 45 years, came to more than $950,000 per sufferer. These data also apply in Europe. In France, 80% of the total cost is due to hospitalization, 3.2% to visits to A&E units, 0.9% to visits to GPs, 3.6% to medication and 11.7% to other specialized nursing or medical treatment.

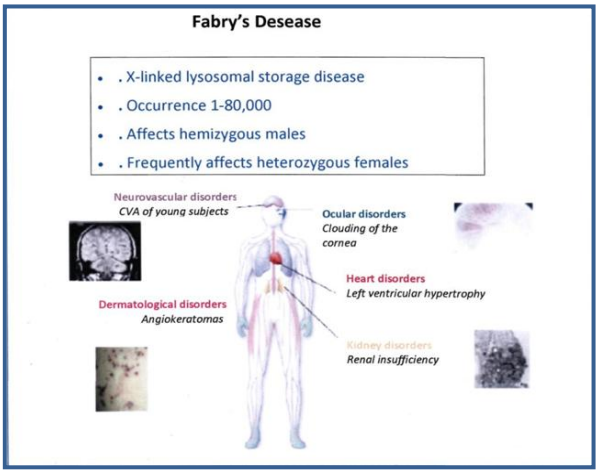
The hearing showed that the development of research was necessary since the study of monogenic and rare diseases was useful for research in more common illnesses.

Since monogenic diseases represent a kind of "measuring rod", they may also serve as a model for the development of new therapies, including for more common diseases such as cancer, diabetes or AIDS. Different forms of treatment, whether they are based on classical pharmacology, gene therapy, cell and/or enzyme therapy, are complementary. Even if certain of these new therapies have not yet been proved to be fully efficient, they are already useful as they help improve the quality of life of patients and allow some of them to survive until a more efficient treatment becomes available. The opposition which has been created by certain people between classical pharmacological therapy and such new therapies is meaningless. Using the latter in no way excludes making use of the former, including the most tried and tested forms of such treatment. These two approaches should now be seen even less in terms of opposition, as some types of gene therapy will now be administered in the same way as classical medication.

Diverse avenues of research to be developed and encouraged

In the research field, many difficulties and shortfalls have been observed. **The continuation of the ban, with a dispensatory clause, on embryo and embryonic human stem-cell research, which was extended by the July 2011 Law on Bioethics, has been unanimously attacked.** The argument which is sometimes put forward that carrying out research with induced pluripotent stem cells (IPS) could avoid using embryonic stem cells is fallacious. The OPECST has demonstrated to what extent this mechanism has penalized research in France. Even though its voice has not been heeded, it shall continue to follow the rules of application as well as the consequences of the passing of this unfortunate ban.

The importance of using animal models, including great apes, which are the only really significant models possible before moving to human clinical tests, was underlined. Attempts by the European Union to strictly limit the use of such models have led to concern.



The lack of biobanks remains an obstacle. These are essential for translational research, as most of these diseases are of a genetic nature with an easily identifiable gene at their origin. In order to advance in this field, it is thus necessary to constitute cohorts of patients who will undergo clinicobiological tests. This requires the stocking of samples in biobanks and enables the assessment of the natural history of such diseases as well as the identification of their molecular bases thanks to genomics, epigenomics, transcriptomics and metabolomics. Thus it would be possible to possess cell or animal models in order to study the most detailed physiopathological mechanisms.

France's lateness in new techniques for genome sequencing is a real drawback. High speed sequencing, which enables the simultaneous testing of all the genes, should be able to allow a much faster identification of the mutations being sought. As regards gene therapy methods, because of a lack of funding, France is considerably behind Germany, Belgium, Spain and the Netherlands, without mentioning the United States or China.

The absence of long-term stable funding with industrial partnerships, the essential corollary of public financing, is not sufficiently taken into account. In fact, there is no other way to develop this type of therapy as far as the medication stage, and investment by the pharmaceutical industry has for the moment is too feeble. All of this despite the

fact that, from an economic point of view, research into rare diseases will certainly not remain marginal.

Ethical and legal issues

Monogenic diseases raise ethical issues on account of their genetic origins. The lower and lower cost of high-speed genome sequencing and the development of diagnostic genetic testing, which can also be predictive, sometimes on open access on the internet, have certainly increased the relevance of such questions.

Genetic information is of a very specific nature in that it deals with the very elements which characterize the individual and link him/her to the family: it plays a role in his/her destiny. In addition, this very detailed knowledge of our genetic predispositions clearly has ethical, legal and societal consequences which must be taken into account. When such information is provided through genetic testing, it may lead to modifications in the conditions in which a person might be insured, hired etc.

What legislation could be considered concerning the use of genetic tests? The legislation would not be the same if the use of genetic testing were to become common or if it were only to concern a very small percentage of the population. The French National Ethics Advisory Committee and the French Agency for Biomedicine are both concerned about the rapid development of the human genome analysis referred to as "recreational genetics" and the proliferation of genetic tests on open access on internet whose reliability cannot be guaranteed.

At the moment, most of the tests available on internet concern diseases which are not monogenic. These are predisposition or susceptibility tests which have no real usefulness from an individual point of view and whose interpretation can change from one day to the next depending on the announcements. This is because in the genome, there are as many genes which protect, as those which weaken and this makes interpretation particularly difficult.

In fact, genetic tests concern various predispositions and pose problems in terms of the care of patients. Who would interpret the result? Which doctor would care for the patient if a medical condition were to be discovered? What is the clinical usefulness of a test which reveals an untreatable predisposition?

For the moment, in the case of genetic tests for monogenic diseases, answers are given in reply to a request. It is thus that in very specific conditions tests have been set up, for example, on Huntington's disease. However, we are now faced with a very new situation: genetic factors will be identified for people who have made no such request. This will be the case for postnatal diagnosis of cystic fibrosis with subsequent tests for the parents and then for the relations of the carriers. This, of course, poses the problem concerning tests carried out on healthy carriers. It will be difficult to ensure that the latter will be in any position to decide if they wish to know the results or not.

The very rapid development of the analysis of the entire genome poses additional questions. What should be done if, when treating a patient with a specific disease, the analysis of his/her genome leads to the discovery of another disease? In genetics, there are sick people and people who are not or who do not feel sick. In addition, we are bound to progress in our analysis of the genome. We must thus anticipate the development of the interpretation of the genome.

The development of genetic tests, such as high-speed genome sequencing, must be seen in the context of the strengthening of social control over the individual. This is a subject which deserves to be dealt with in greater depth. The easier it becomes to sequence the entire genome of a person and the less costly it becomes to do so, the more important it is to protect such data in order to ensure that they are not used for reasons other than medical or scientific ones. This is even more difficult given that the globalization of biology makes it almost impossible to ensure that what is strictly regulated (or even prohibited) in one country, cannot be carried out, often at a very cheap price, in a system with more negligent or even inexistent regulation. In this respect, the French Agency for Biomedicine plays its role by providing information and follow-up on the use of genetic tests on open access on the internet. However, is this a sufficient deterrent?

These questions were raised by members of the OPECST who were travelling on missions concerning other issues, particularly in the United States and the United Kingdom. They worry patient associations, geneticists and legal experts from various countries. The international instruments for the protection of persons, such as the Convention on Human Rights and Biomedicine

(Oviedo Convention) which France has just finally ratified through article 1 of the July 2011 Law on Bioethics, make provision for a general level of protection which is not yet sufficient. Coupled with this, an additional protocol specifically pertaining to genetic tests for medical reasons was drawn up and available for signature as of November 2008. It has not yet entered into force although France, which actively participated in its drafting, has signed it. An instrument which is currently being drawn up at the Council of Europe concerns the predictability of genetic tests and the impact upon insurance. France is participating at a high level in its drafting as it presides over the Committee on Bioethics of the Council of Europe (DH-BIO). Such efforts must be supported.

In France, the Code of Civil Law provides that "no one shall be subjected to discrimination on account of his/her genetic characteristics" and this prohibition is repeated in the Codes of Criminal, Labour, Insurance and Social Security Laws. In the case of the results of a test, the problem of the transmission of information to the next-of-kin is delicate, especially if the person does not wish to disclose information to his/her family which might be important for them. This question was dealt with in a balanced manner by article 2 of the July 2011 Law on Bioethics. However a follow-up on the implementation of these provisions is necessary.

This public hearing demonstrated the need to continue to study the impact of high-speed gene sequencing and underlined the field of reflection to which the OPECST itself should contribute.

Recommendations

Several avenues can be identified to ensure an appropriate treatment of these diseases. These would entail:

- gathering precise figures and data (no assessment of the cost for society of rare diseases has ever been carried out);

- identifying priorities and ensuring that financial resources are equitably shared;

- not neglecting any therapeutic approach and avoiding having various therapies badly used or diverted from their original medical or scientific aim;

- supporting the setting up of the "Rare Diseases" Foundation whose establishment was announced by the Government for 2011 but which actually took place on March 7, 2012. This support should be given because the Foundation's aims correspond to a strong request both by patients and by medical staff;

- rapidly implementing the 2nd National plan on "Rare Diseases" presented on February 28 2011 (after the first plan 2004-2008), as its aim is to set up genuine national structures for diagnosis and care;

- encouraging the setting-up of a national database for rare diseases gathering the clinical data from the reference centres and the biological and therapeutic data from other bases in order to ensure the rapid identification of the patients eligible for a newly started therapeutic trial or to find the correlation between certain clinical disorders and certain genetic disorders;

- bringing together funding at a European level by setting up a European research body attached to the Directorate General "Research" of the European Commission. This body would gather all existing databases and would enable the creation of a true European database on rare diseases;

- participating more actively in the harmonization of rules and practices at an international level.