Opinion concerning the identification of patients suffering from glaucoma in France and on chromosomal location of the causative gene or genes

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Opinion

The *Comité de Lutte contre le glaucome* (Committee to combat glaucoma) requested this opinion.

The National Consultative Ethics Committee for Health and Life Sciences (CCNE) recalls:

- CCNE's Opinion dated May 6th, 1985, on medical registries for epidemiological studies.

- CCNE's Opinion dated June 24th, 1991, regarding the application of genetic testing to individual studies, family studies, and population studies.

- the law dated January 6th, 1978 on Computerisation, Records and Liberties

- the law dated December 20th, 1988, modified on January 23rd 1990, on the protection of individuals contributing to biomedical research.

Progress in the field of genetics has brought about broad family studies for the purpose of analysing the role of genetic components in common diseases. In these diseases, we find on the one hand highly familial forms in which Mendelian type inheritance patterns are suspected or demonstrated, and on the other hand and much more frequently, isolated forms which are not indicative of genetic determination.

Chronic open-angle glaucoma and juvenile glaucoma are one example. They represent an important public health problem. It is therefore logical that studies should be undertaken to evidence, if that is the case, genetic traits which either govern or have an influence on the appearance of this disease.

The objectives stated in the request submitted by the Comité de Lutte contre le glaucome to CCNE read as follows: " *identifying patients suffering from glaucoma in France, screening for undiscovered cases, and locating the causative gene or genes so as to develop new therapy and prevention through systematic blood test screening" .*

The CCNE's June 24th 1991 Opinion recalls that familial and epidemiological investigations based on genetic tests must conform to *ordinary ethical rules* :

- respect for an individual's autonomy; he is entitled to facts permitting informed consent,

- respect of the right of those tested to know or not to know the results, the significance of which will have been clearly explained,

- respect for the confidential nature of genetic information, privacy, and medical secrecy.

In fact, the conditions in which it is proposed to carry out the study transgress the above principles on several points, and also some *important rules of deontology* :

- nominative and sensitive data concerning members of the glaucoma patient's family (suicides, depressions) is requested, but the letter given to patients only states: " as regards living members of your family, CNIL(1) wishes you to ask for their consent before revealing their identity" . This wording is obviously inadequate and should be replaced by " it is *indispensable* that you obtain consent from members of your family suffering from one or other of the conditions referred to in the questionnaire before revealing their identity" .

- the family facts sheet asks for the name and address of the attending physician, which arouses the suspicion that he might be involved in the enquiry at some later date, particularly since some of the information patients are asked to supply is so technical that they are unlikely to be able to give it correctly on their own.

If that was the case, articles of the Code pénal governing medical confidentiality would be violated, as would also articles 11 and 13 of the French medical code of deontology.

Rules in the code of deontology which all physicians must obey, cannot contain any contradiction of existing legislation.

As long as a law on processing nominative data for research aiming to protect or improve health is not enacted, intrusion of a doctor on a member of the family, frequently a distant relative, could lead to a complaint to disciplinary bodies, particularly if questions on particularly sensitive matters were asked, such as manic-depressive diseases or abnormal behaviour.

Sanctions written into the *Code pénal* or those of disciplinary bodies could be inflicted on doctors acting against these rules.

On the *scientific aspect* of the programme submitted, it appears that it could not respond to questions investigated. The scientific objectives are the following: is there a genetic mode of transmission of one or all forms of glaucoma? Are there associations with other affections?

Such research must be conducted according to rigorous methodological criteria:

1- Define the nosology of glaucoma and of affections with which it might be associated;

2- Use genetic epidemiological methods adopted for the study of common diseases with genetic components, because it is speculative to extend results obtained by observation of a few familial forms to other frequent forms of the disease;

3- Only embark on molecular biological studies once rigorous epidemiological studies are completed. So far, there is no scientific evidence to the effect that juvenile glaucoma is a single-gene disease.

As regards the objective of early diagnosis for effective prevention of the disease, it should be said that this object can be achieved by measuring intraocular pressure systematically in all routine eye examinations, in particular from the age of 40 upwards, followed by information on collateral relatives of patients. National registration of all glaucoma patients would not improve the quality of prevention.

For all the above reasons, the National Consultative Ethics Committee is expressing an unfavourable opinion on the implementation of the study as planned by the petitioners.

Report

For a certain number of common diseases (diabetes, cancers...) there are forms where a strong familial concentration or a Mendelian type heredity is either demonstrated or suspected, on the one hand, and far more frequently, isolated forms which do not clearly point to genetic determination.

It is extremely speculative to extrapolate results drawn from observation of a few familial forms to other frequent forms of a disease. Thorough epidemiological genetic and molecular biology studies are necessary to establish that the various forms share the same etiology.

Glaucoma is one example of these difficulties. It is the result of intraocular pressure, the consequence of which is progressive destruction of the cells of the retina and of the optic nerve, leading to field loss and blindness.

There are acute forms, infantile glaucoma and closed angle glaucoma, which are ophthalmic emergencies.

The most *frequent* of the chronic forms is *open-angle glaucoma* which is found in 1% of the population over the age of 40. Diagnosis is arrived at by systematic checks on intraocular pressure whenever the eye is examined. Early diagnosis makes it possible to prescribe simple medicinal therapy which stabilises intraocular pressure so that extension of cellular damage and blindness can be avoided.

This is the most *frequent* glaucoma, but a rarer and earlier form, called juvenile glaucoma, exhibits few symptoms at first but blindness ensues. The gravity and the insidious onset of juvenile glaucoma make early diagnosis desirable. Contacting young individuals at risk before any serious damage is done is very important because although therapy may stabilise the situation, damage once done is irreversible.

Chronic open-angle and juvenile glaucoma are therefore important public health problems. It was therefore a logical step to undertake genetic research to discover any genetic traits which govern, or at least influence the occurrence of the disease.

Research strategies

1. Epidemiological studies

Inherited traits for glaucoma and association to other ailments

Observation of familial cases have for a long time given rise to speculation about a genetic factor in the transmission of glaucoma.

The most documented cases of inherited glaucoma concern juvenile glaucoma. Previous publications (J. François *: l'Hérédité en Ophtalmologie* ; V. Mckusick: *Mendelian inheritance in man* ; A. Emery and D. Rimoin *: Principles and practice of medical genetics*) reported familial juvenile glaucoma with mostly regular dominant transmission, but other familial cases seemed closer to recessive inheritance.

These observations report exceptional families in which appearance of glaucoma before the age of 30 drew attention.

With chronic open-angle glaucoma, familial observations are difficult because the condition

is discovered late in life so that reference to cases in earlier generations has to be based on reported case histories instead of direct observation, and some of the siblings may have died before symptoms were visible.

Some studies which have been published on chronic glaucoma series report about 15% familial cases (2 cases or more).

Sensitivity to cortisone has been found by testing with dexamethasone (measuring intraocular pressure for six weeks, after instillation of eyedrops containing dexamethasone three times a day). Similar response in diabetics led to investigation of a possible association between chronic glaucoma and diabetes. The only important study, published in 1973, stated in its conclusions: *" it can legitimately be stated that there is a common genetic transmission of chronic open-angle glaucoma and diabetes in a polygenic mode where gene PH (sensitivity to cortisone) seems to be one of the components of this transmission" .*

Since that study was made, 20 years ago, no other study has reported any association between glaucoma and diabetes, still less other conditions (manic-depressive psychosis, migraine....).

Epidemiological studies are hampered by the nosological imprecision of the diseases concerned. There is hesitation about where to classify juvenile glaucoma and there are several kinds of diabetes. Diagnosis of manic-depressive psychosis is difficult enough when the patient is alive; for preceding generations it becomes impossible.

2. Demographic studies

The method is to go back to a *" common ancestor* " , and then descend to all descendants.

Apart from nosological difficulties encountered in epidemiological studies, there is always a doubt about biological filiation.

Even supposing the " *common ancestor* " has been identified, an analysis of descendants is not very effective. Is a reminder necessary that with autosomal dominant inheritance, one child in two does not inherit the mutated gene, and is therefore healthy, so that in each generation the risk of finding an affected individual is divided by two, progressing from 1/2 to 1/4? After ten generations, the risk is 1/1024, whereas the frequency of late onset open-angle glaucoma in the population at large is at a higher figure.

3. Molecular biology studies

These can only be undertaken once rigorous epidemiological studies have been completed.

For well defined single-gene affections, extensive familial studies made it possible to locate the mutated gene on a chromosome segment, to trace transmission of this gene in families using molecular markers closely connected to the gene, and in a few cases, to isolate and characterise the gene, and then the protein.

There is to-date, however, no scientific proof whatsoever that juvenile glaucoma is a single-gene disease. Another research strategy will therefore have to be found.

Furthermore, even if the single-gene hypothesis were to be confirmed, the first requirement would be polymorphic markers genetically linked to, but different from, the gene of the disease.

The probability of recombination occurring between such markers and the morbid gene since the period of time when the " hypothetical common ancestor" was alive, would make it

necessary to verify, in each individual family, to which marker the morbid gene is linked. In other words, a detailed family study would have to be made for each case. It would only be when at some point in the distant future the hypothetical " glaucoma gene" was isolated and a unique (or very predominant) mutation had been discovered for that gene, thus marking a founder effect (i.e. descent from a common ancestor) that simply exploring the DNA of white blood cells in a blood sample could suffice to detect carriers of the genetic defect.

Request submitted to CNIL in 1992

Based on the assumption that glaucoma is a disease with a strong genetic component, a census of all glaucoma patients in France is proposed. Patients would be advised to warn members of their family of the risk and to recommend that they should consult an ophthalmologist systematically. In parallel, information supplied by patients and their families would help to study the mode of transmission of glaucoma and association to other diseases: diabetes, manic-depressive syndrome, and migraine. According to the petitioners, the study would even make it possible to locate the gene or genes involved.

The project has therefore a double aim: prevention and fundamental research.

In scientific terms, the proposed approach, i.e. exhaustive census of patients, has almost no chance at all of producing results because of its gigantic nature, the inevitable lack of accuracy as regards in particular the definition of phenotypes of the various affections concerned, and the fact that the molecular biology branch of the work is superficial.

From the point of view of public health, an exhaustive census of glaucoma patients in France also seems unreasonable.

As regards respect for the code of deontology - by decree of the *Conseil d'Etat* - which is an obligation on all physicians, two points must be made.

1) The letter given to the patient reads " it is necessary that patients obtain their relatives' consent prior to disclosing nominative data" .

This commitment is essential to comply with deontology. In the " family facts sheet" which was submitted, a whole page is devoted to members of the family (including nephews and nieces, or distant relatives) affected now or in the past by: glaucoma or hypertonia oculi, diabetes, depression, suicide. The husband's name or maiden name, first name, degree of kinship on the mother's side or the father's, are to be filled in.

However, in the letter which is handed to glaucoma patients participating in the enquiry, it is specified that " as regards living members of your family that you mention as being affected by one or other of these diseases, the Commission Nationale de l'Informatique et des Libertés wishes you to ask for their consent before revealing their identity" . This discrepancy is worrying.

2) In the same " family facts sheet" , is written:

"your attending ophthalmologist: Doctor...., name and full address."

In article 2 of the project for the computerisation of research on a census of glaucoma patients in France, a sub-paragraph reads, inter alia, " source of case notification: name of the attending physician" .

Such precautions are, at best, superfluous (there is no risk of duplication when the name of the patient is not coded). At worst, they are unacceptable - the attending ophthalmologist is likely to be consulted since the patient is asked to state whether the case is " an exfoliation syndrome, a pigment dispersion syndrome, or a mixed glaucoma" .

In this case there would be a violation of the Code pénal (article 378, old code, or article 226-13 of the revised code) and of articles 11 and 13 of the French code of medical deontology.

In conclusion

Glaucoma raises two sets of extremely interesting problems:

- **scientific problems**

What is the mode of transmission of glaucoma or of its various forms?

Are there any associated affections?

Such research must be conducted according to rigorous methodological criteria.

1- For glaucoma and possible associated affections, the nosological framework is not as yet well defined and no consensus has been reached.

2- Epidemiological genetic methods adopted for the study of common diseases with genetic components must be used.

3- Molecular biological studies can only be considered once the first two conditions have been fulfilled.

In order to tackle this problem, a rigorous study of several families would have to be made, with the assistance of ophthalmologists, and medical specialists in genetics, molecular biology, and epidemiology. Pilot case studies could probably also be considered.

- **a public health problem**

Measuring intraocular pressure must be included in all eye examinations particularly from the age of 40 onwards. This simple routine examination should suffice to effectively prevent the consequences of open-angle glaucoma, far and away the most frequent form.

Discovery of juvenile glaucoma should give rise to warning collateral relatives with the practical aim of detecting asymptomatic patients. There is no necessity however to make a census of glaucoma cases.

Should also be recalled the CCNE's Opinion of 24th June 1991 on the application of genetic testing to individual studies, family studies, and population studies (DNA " banks" , cell banks, and computerisation of data problems). Any such research should refer to that Opinion.

Notes

1. Commission Nationale de l'Informatique et des Libertés (National Commission for Computerisation and Liberties)