Reports of Investigation

Clinical reassessment of malignant hyperthermia in Abitibi-Témiscamingue

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Purpose: In 1992, 1812 individuals (1.2% of the population) were labelled at risk for malignant hyperthermia (MH) in seven families from Abitibi-Témiscamingue. To evaluate the effective risk in this population, a multidisciplinary study was undertaken which included clinical, genealogical and molecular aspects. This paper presents the clinical aspects of the study.

Method: For each of the 1546 individuals reached, all anaesthetic exposures were screened for elements relevant to MH. Malignant hyperthermia events were analyzed with "the clinical grading scale." All 44 reports of caffeine halothane contracture tests were reappraised. Finally, a genealogical study was done to complete each family tree up to the initial French settlers in order to identify links between these seven families through common ancestors.

Results: Following this reassessment, the families were compared and classified into four groups. Two families (1097 individuals) are not considered to be at a higher risk for MH than the population in general. Two families are still considered possibly at risk. Finally, one family (402 individuals) is highly at risk and two other families are probably at risk. Family trees did not show any link up to the colonization of Abitibi-Témiscamingue in the beginning of this Century but common ancestors were found around the 9th generation.

Conclusion: This clinical reassessment will help to focus education and prevention on a much smaller group of individuals still considered potentially at risk for MH. By adequate evaluation of phenotypes, combined with the use of a genealogical approach, it will be possible to target families for molecular research.

Objectifs : En 1992, 1812 individus (soit 1.2% de la population) étaient étiquetés comme susceptibles à l'hyperthermie maligne (HM) dans sept familles de l'Abitibi-Témiscamingue. Afin d'évaluer le risque réel de cette population, une étude multidisciplinaire fut initiée incluant les volets clinique, généalogique et moléculaire. Cet article présente les aspects cliniques de cette étude.

Méthode : Pour chacun des 1546 individus rejoints, toutes les procédures anesthésiques furent évaluées afin de retrouver des signes révélateurs d'HM. Les épisodes d'HM furent examinés à l'aide d'une échelle de gradation clinique. Les 44 rapports révisés de tests de contracture caféine-halothane furent pris en considération. Finalement, une étude généalogique de chaque ascendance, jusqu'aux premiers arrivants français, fut menée afin d'identifier les liens entre ces sept familles à travers des ancêtres communs.

Résultats : Suite à la révision clinique, les familles furent comparées et classées en quatre groupes. Deux familles (1097 individus) ne sont pas considérées plus à risque que la population en général. Deux autres familles sont encore considérées comme ayant un risque possible. Finalement, une famille (402 individus) est considérée hautement à risque et deux autres familles sont classées comme ayant un risque probable. L'examen des ascendances montre qu'on ne retrouve pas d'ancêtres communs aux cas avant la 9^e génération. Ces ancêtres communs ne sont pas originaires de la région; en effet, celle-ci a été ouverte à la colonisation vers 1900 soit depuis 3-4 générations seulement.

Conclusion : Cette révision clinique permettra de concentrer l'éducation et la prévention vers un groupe d'individus encore considéré potentiellement à risque pour l'HM. En évaluant mieux les divers phénotypes, en combinaison avec l'utilisation d'une approche généalogique, il sera possible de cibler les meilleures familles pour la recherche en génétique moléculaire.

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MALIGNANT hyperthermia (MH) is an inherited musculo-skeletal disorder in which susceptible individuals may develop a potentially fatal reaction when exposed to triggering anaesthetic drugs (halogenated anaesthetics and/or succinylcholine). The prevention of new MH reactions depends primarily on proper information and education of individuals and families at risk for MH.^{1,2}

Abitibi-Témiscamingue is a region of North-Western Québec (population: 150,000). In 1970, after the first MH fulminant fatal reaction in the region, a hospital-based list of family names was created. In the largest of the five hospitals, creatine kinase (CK) blood levels were measured for the majority of patients requiring surgery. On this basis, or following MH reactions, several patients (identified in nine families) were labelled at risk for MH. Over the years, many members of these families volunteered for diagnosis using the caffeine-halothane contracture test (CHCT).

In 1992, 1,812 individuals were believed to be malignant hyperthermia susceptible (MHS). To re-evaluate the MH risk in this population, an epidemiological approach which included every family member was used to study all previous anaesthetic exposures and MH reactions. Such an approach may enable clinicians to reassure some families which are not truly at risk for MH and to emphasize education and prevention in confirmed MHS families. For researchers, this approach may help to focus on families with a true MH phenotype.

In specific MHS families, studied by different research groups, at least four chromosomal loci (chr. 19, 17, 7 and 3) may be associated with MH.³⁻⁶ The French-Canadian population, upon which our study is based on, descends from approximately 8000 French settlers and is recognised as an excellent research model for genetic studies because of this so called "founder-effect." Indeed, when a small group immigrates from a mother population, a rare allele in this mother population may be present in one or a few of these immigrants and is transmitted to their descendants. Moreover, this research model is well documented demographically and genealogically due to the excellent quality of the Roman Catholic parish registers since the beginning of the colonization in early XVIIth Century.

Since phenotype analysis of MH may confuse research in molecular genetics,⁷⁻⁸ we believe that an accurate determination of each phenotype through clinical evaluation combined with the genealogical approach should help to plan the molecular analysis better. By using a careful clinical re-evaluation of all

cases in a given region, followed by a comprehensive study using population genetics and genetic epidemiology, one may hope to improve understanding the MH risk in this population and, eventually, to help the development of a specific molecular genetic diagnosis. This article is limited to the first phase of this pilot study, the clinical re-evaluation of all French-Canadian MHS families in Abitibi-Témiscamingue.

Methods

Patients

After approval by the hospital Ethics Committee and using the pre-existing hospital-based MH list, all probands (individuals at the origin of the familial investigation) were contacted. Then, individuals with CHCT results were also reached. They all consented to participate in the study and helped us to contact their relatives. Through family reunions, individual meetings, phone calls and letters, we obtained the participation of 100% of the individuals reached. All the participants signed authorizations to release information concerning their previous anaesthetic procedures performed in hospitals within or outside the region. When necessary, patients signed a form to obtain their original CHCT report and its reappraisal. The MH Investigation Units did their own reappraisals following the guidelines defined, in 1989, by the North American Malignant Hyperthermia Registry (NAMHR) to standardize the CHCT on skeletal muscle biopsies.⁹ Finally, in addition to information regarding their blood relatives, short family trees were drawn by family members (two to three generations). Afterward, the complete ascending family tree of each proband was built up to the initial French settlers in North-America (early 17th Century) by our genealogical experts, in collaboration with Programme de Recherche en Démographie Historique at Université de Montréal.

Review of medical charts

For the 1,812 individuals initially identified, 2,073 medical charts were retrieved within or outside Abitibi-Témiscamingue and 1597 procedures under general anaesthesia (GA) were found. Every exposure to GA was identified and reviewed and for every suspected MH event, the chart was reviewed using the clinical grading scale developed by Larach *et al.*¹⁰

A structured datasheet was used which included the following items: name, hospital, number and type of surgery, urgent or elective procedure; and, for each exposure, the anaesthetic agents, length of anaesthesia and surgery, monitoring, unusual events noted by the anaesthetist, unusual monitoring values. Finally, over-

all evolution during hospitalisation was noted (infection or other complication), length of stay in hospital, and any special comment on the procedure itself. These data were then recorded in a database using the ANALYPOP software (F.-M. Mayer, Université du Québec à Montréal). This biomedical database was added to another developed for genealogical analysis. These two databases were managed separately in order to maintain confidentiality.

Results

For the initial 1,812 individuals identified, 1,010 are still in the region, 315 are living elsewhere in Québec, 221 outside Québec (mainly Ontario), and 266 have not yet been localized. The follow-up process is still in effect for these 266 individuals. Of the nine families initially identified, two were studied together, as the probands were found to be cousins. Since our study is limited to French-Canadians, one family (28 individuals) of British descent was not included for research purposes but was clinically reevaluated and a follow up was made.

For this paper, seven families are described and compared (Tables I, II and III). The results obtained to date describe a special anaesthetic and biological (CHCT) profile for each of them:

Family A: In Abitibi-Témiscamingue, the MH problem was first identified in this family (cf. Table I: proband A). Five MH events have been found and 402 individuals have been studied. Using the clinical grading scale,¹⁰ three of the five MH events (one death in 1970 and two crises in 1968 and 1969) scored six (almost certain MH). Two MH deaths (aunt of the proband in 1959 during a cholecystectomy, and a first degree cousin of the proband in 1971 during a hysterectomy) could not be reviewed as their charts had been destroyed. For this family, only 88 exposures to triggering agents (79 before 1972) were found (Table III) and no other MH event has been reported for the individuals reached in this study. As shown in Table II, 21 CHCTs were revised and, according to the NAMHR criteria, eight are still considered positive. No evidence of muscular disorder was detected, except for muscle cramps in a few members of this family.

Family B: This family contributed 1,058 individuals to the database (54.7%). The clinical grading scale was used for the first proband and ranked 0: no exposure to GA could be found for the other so-called proband. From 1973 to 1981, preoperative CK measurements were routinely performed in this family. The CKs were slightly elevated ($< 1.5 \times \text{Normal}$ (1.5N)) in a few instances and were the sole reason for a CHCT. The

chart revision showed that a large number of the procedures under GA were done with triggering agents even after an MH problem was suspected in the family (92% of all GAs before identification of MH problem and 82% of all GAs after). No MH event ever occurred (Table III). All 16 CHCTs were reviewed and found to be negative (Table II). No muscular problems were mentioned in this family.

Family C: This family includes only 39 individuals. No anaesthesia problem could be found in the proband's chart. On the basis of slightly elevated preoperative CKs, he was later referred for CHCT and this test was found to be positive. The reappraisal of this CHCT changed its interpretation to a negative result. The chart review for this family did not show any evidence of MH. It should also be noted that the proband was a drug addict (cocaine, hashish, etc) and it has been found that this may affect CHCT results.¹¹ His CKs were also elevated when intoxicated.

Family D: The proband did not have any MH event in his three exposures to triggering agents. The chart review showed an elevation of preoperative CKs (2N) and other hepatic enzymes, on one occasion, but the patient had cholecystitis at that time. He was then anaesthetized without triggering agents and later referred for a CHCT. Even after revision, this CHCT is still considered positive. All the anaesthesia charts of this family were analyzed and no MH problem was found, despite the fact that these individuals were exposed to triggering agents even after the MH problem was suspected. Only the proband had a CHCT. However, some muscular problems are found in this family: muscular dystrophy (type not yet identified) in a nephew of the proband and some cramps in three other individuals.

Family E: The family group studied is very small (11) because all other members are living outside the region and keep no contact. The proband was referred for CHCT due to repeated isolated elevated CKs (10N). She also presents elevated hepatic enzymes. The charts did not reveal any problem with anaesthesia. Contacts outside the region were made by the proband herself and it appears that no event is known in that family. Two CHCTs were done (proband and her sister). Only the proband's CHCT was positive and still is after reappraisal.

Family F: In 1989, an eight-year-old boy survived an MH crisis ranking six. The child was submitted to a CHCT and is still positive after reappraisal. To date, neither of his parents have agreed to have a biopsy performed. The whole family was investigated and no

other anaesthetic problem was found. About 80% of GAs were done with triggering agents (Table III) but mostly before identification of the MH problem. No muscular problem was found in this family.

Family G: In 1993, a six-year-old boy survived a MH crisis ranking five (48 points). This child is still too young to have a CHCT; his parents were asked to have a CHCT and refused. All the anaesthesia charts were reviewed for this family (146 individuals) and nothing unusual was discovered, even though they had been exposed many times to triggering agents before identification of the MH problem (92.1% of all GAs).

Discussion

As all probands and their relatives accepted participation in this study, collaboration was exceptional. Since only a few individuals had a CHCT, many members of these families were labelled MHS on the basis of the family history. They were eager to help us clarify the MH problem in their family.

In Québec, medical records are not destroyed after a defined interval as in other countries and provinces (e.g., 10 years in Ontario), and so, suspicious MH events could be retrieved more easily in the charts. As the region has a limited number of anaesthetists (15) and hospitals (5), details regarding old anaesthetic

TABLE I Probands

Proband	Year	Age	Sex	Surgery	MH problem	Triggers	Previous exposure*
A	1970	40	F	Cholecystectomy	Death	Halothane	0
B	1973	13	M	↑ Preop. CKs	—	—	0
C	1973	17	M	↑ Preop. CKs	—	—	1
D	1974	37	M	↑ Preop. CKs	—	—	3
E	1984	30	F	↑ Preop. CKs	—	—	1
F	1989	8	M	Tonsillectomy	Crisis	Halothane + Succ.	1
G	1993	6	M	Knee Arthroscopy	Crisis	Halothane + Succ.	1

*Previous exposure to triggering agents

TABLE II CHCT Results

Family	Original results		Reappraisal by Biopsy Centers		Reappraisal according to NAMHR criteria*			
	+	—	+	—	+ complete	+ incomplete	— complete	— incomplete
A	15	6	8	13	1	7	3	10
B	10	6	0	16	0	0	3	13
C	2	1	0	3	0	0	1	2
D	1	0	1	0	1	0	0	0
E	1	1	1	1	0	1	0	1
F	1	0	1	0	1	0	0	0
G	0	0	0	0	0	0	0	0

*In 1989, standardization of the CHCT was achieved in North America. Since the actual study has to deal with CHCTs performed long before that date, a classification was made. In order to be complete, the muscle strips had to be exposed to halothane 3% and 2mM caffeine. If one or both of these tests were not done, then the CHCT will be considered incomplete.

TABLE III Medical Records

Family	Number of individuals: male/female	MH Death	MH Crisis	↑CKs	Number of charts reviewed	Number of general anaesthetics	Number of GA with triggering agents
A	201/201	3	2	—	265	158	88
B	537/521	—	—	>10*	1879	1016	873
C	25/14	—	—	1	65	49	40
D	30/21	—	—	1	112	84	71
E	3/8	—	—	1	7	4	3
F	52/53	—	1	—	230	122	98
G	80/66	—	1	—	275	164	151

*10 results found in the charts, but over 100 patients reporting CKs in the past.

practices could also be retrieved more easily. On the other hand, it rapidly became evident that many familial anaesthetic histories were not based on events that could be confirmed by the charts. For example, fever reported by a patient did not develop during or immediately after the surgical procedure, but was found only days afterwards.

In four families (B, C, D, E), it was found that exposure to triggering agents continued for many years, as the information about possible MH susceptibility was not given to all members of these families. As information was given, fewer GAs with triggering agents were performed. Analysis of these exposures over the years was very useful to our research. For the two families with recent MH crises (Families F and G), few anaesthetic procedures were performed after the discovery of MH and safe techniques were then used. Within a few years after discovery of the MH syndrome, only safe anaesthetic techniques were also used for members of family A.

After analyzing each family group and its characteristics, a classification of the families was done for clinical purpose and also for future research analysis with genetic epidemiology and molecular biology:

- Group I : Highly at risk (family A)**
Several deaths and crises
Many CHCTs still positive
402 individuals studied
- Group II : Probably at risk (family F and G)**
No death but MH crises (rank 5 or 6)
Proband F (positive CHCT)
Proband G (no CHCT, only nine years old)
105 and 146 individuals studied respectively
- Group III: Possibly at risk (family D and E)**
No death nor crisis but only increased preop. CKs
Proband D and E (positive CHCT)
Only 51 and 11 individuals studied respectively
- Group IV: No more risk than general population (family B and C)**
No death nor crisis but only increased preop. CKs
All CHCTs negative
1,058 and 39 individuals studied respectively

For clinical purposes, patients from Group I, II, and III must be treated with safe anaesthetic agents for MH. Families in Group IV do not have any evidence of an increased MH risk compared to the gen-

eral population and standard anaesthetic care is adequate. As some patients in Group IV might still be reluctant to be exposed to triggering agents, a trigger-free anesthesia could then be used in order not to increase their anxiety before a surgical procedure. Obviously, education of these patients should take place after surgery.

For research purposes, family A is considered a certain example of an MH pedigree but in Abitibi-Témiscamingue the two survivors of MH crises ranking six have not yet been investigated, having refused to submit to CHCT. In families F and G, even if the probands had MH crises ranking five or six, only one CHCT has been performed (proband F) and all other members of these families have refused to have this test performed. In families D and E, no MH problem could be found except a positive CHCT for the two probands. As some other muscular problems may give a positive CHCT,¹²⁻¹⁴ this may explain the CHCT results for proband D. Since the specificity of the CHCT in North America is currently believed to be 78%,¹⁵ the historical use of CHCT solely on the basis of increased preoperative CKs (without an associated anaesthetic problem) could have falsely labeled 22% of these individuals as MHS.

For Abitibi-Témiscamingue, the systematic screening of all anaesthesia exposures for complete MH families helped to evaluate the risk and the extent of the MH problem in this population. From the initial 1,812 individuals labeled MH susceptible, only 715 are still considered potentially at risk. A screening bias in the 1970s and early 1980s is partly responsible for the high percentage of individuals labeled MHS in this regional population. The population of Abitibi-Témiscamingue is probably not more at risk than the general population of Québec. However, other regions seem at higher risk and are being investigated. Based on firm clinical signs, provided by an extensive phenotypic evaluation and classification of MH families in Abitibi-Témiscamingue combined with genealogical analysis, molecular genetic studies will now be initiated.

Besides the clinical reappraisal, the complete genealogical study of the families at risk is an important part of the global evaluation of MH in Abitibi-Témiscamingue. Preliminary results show that there is no common ancestor who can be traced in Abitibi-Témiscamingue (founder effect), which is not surprising, since the region was colonized less than 100 years ago. Common ancestors to probands were not found before the 8th or 9th generation, which could be explained by the fact that families migrating to Abitibi-Témiscamingue at the beginning of this

Century came from different regions of Québec. Using the same multidisciplinary approach, our group is studying MH families from several well-defined regions of Québec (denominative survey conducted with anaesthetists of the Province). The actual French-Canadian population originates mostly from approximately 4000 couples of initial settlers. It is possible that a genetic link at a molecular level could be found within the French-Canadian MH families, and that it could be possible to identify a pattern of distribution of MH in Québec.

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