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Short Communication

Presymptomatic Diagnosis in Retinal Vasculopathy with Cerebral Leukodystrophy

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Abstract

Genetic counselling and pre-symptomatic diagnosis (PD) have been scarcely investigated in monogenic hereditary cerebral small vessel diseases, including retinal vasculopathy with cerebral leukodystrophy (RVCL). We describe the sociodemographic characteristics, motivations and the recent outcome of PD in subjects at risk of RVCL in four-generations of a large genealogy where three related-clinical cases were previously confirmed by molecular tests. Participants were studied based on three strategies: screening for *TREX1* gene mutation, a health education session, and genealogy study of the families involved. A multidisciplinary team participated in the PD program, including neuro-geneticists, neurologist, social workers, psychiatrists and neuropsychologists. Only 11 related-subjects requested for a PD of RVCL. The distribution of gender in the participants was equal, six participants had not a stable relationship, and the remaining five already had offspring and partner. Participants in the PD were of similar sociocultural level. After neuropsychological testing and psychiatric interview, only 8 out of 11 people were given the results, six individuals were positive for the mutation and two negatives. The remaining three individuals were referred for psychiatric attention due to symptoms of depression and anxiety. After having improved from his depressive symptoms, one of these subjects received his positive genetic result. Some months later, another asymptomatic relative visited us to request her result; but she did not come back. The presence of consanguinity in two marriages raises new ethical dilemmas for geneticists.

Three subjects dropped-out after the first step of the procedure in this study, which is in agreement with the percentage reported for similar disorders. These initial data in familial RVCL show that PD is requested and that there is high dropout rate. The main motivation to ask for PD in RVCL was to plan their future based on their genetic information. Based on our experience, we followed a multistep procedure for genetic counselling and PD for RVCL in order to obtain minimal harmful consequences of genetic testing and a high psychological well-being after the PD process.

Keywords: *Retinal Vasculopathy with Cerebral Leukodystrophy; Pre-Symptomatic Diagnosis; Genetic Counselling; TREX1 Gene Mutations*

Abbreviations

MRI: Magnetic Resonance Imaging; CADASIL: Cerebral Autosomal Dominant Arteriopathy with Silent Infarcts and Leukoencephalopathy; CARASIL: Cerebral Autosomal Recessive Arteriopathy with Silent Infarcts and Leukoencephalopathy; RVCL: Retinal Vasculopathy with Cerebral Leukodystrophy; PT: Presymptomatic Tests; PD: Pre-symptomatic Diagnosis; CNS: Central Nervous System

Introduction

Monogenic hereditary cerebral small vessel diseases represent 5% of patients with vasculopathies, which are characterized by lacunar strokes and white matter hyperintensities on magnetic resonance imaging (MRI), and infarcts. Among these diseases we can include: cerebral autosomal dominant arteriopathy with silent infarcts and leukoencephalopathy (CADASIL) [OMIM#125310], cerebral autosomal recessive arteriopathy with silent infarcts and leukoencephalopathy (CARASIL) [OMIM#600142], Fabry disease [OMIM#301500], COL41A-related disorders [OMIM#611773], and retinal vasculopathy with cerebral leukodystrophy (RVCL) [OMIM#192315] [1-3]. These disorders are difficult to diagnose as they are rare entities, a multidisciplinary team is required, and physicians must thoroughly explore the family history of the patient. To date the molecular test identifying the mutation of known disease-causing genes, when available, is fast, reliable and considered as the gold standard for its diagnosis.

Once the molecular diagnosis is confirmed, it would be appropriate to offer genetic counselling to the patients and their relatives, and pre-symptomatic diagnosis (PD) as well, when is solicited by subjects at risk. Testing unaffected individuals at high risk requires that the clinician accomplish with international guidelines provided by professional and regulatory authorities regarding pre-test counselling and written consent.

Molecular testing can assist in making a diagnosis in an affected subject, but may also provide useful information for risk for unaffected relatives. For instance, in some cases; it has been documented that PD may offer psychological well-being and family satisfaction levels long-term after being confirmed as carriers for gene mutation causing a neurodegenerative disorder [4].

We have recently published the clinical and molecular characteristics of a large Mexican family with RVCL carrying *TREX1* gene mutation [5]. Herein, we want to describe our experience offering genetic counselling and pre-symptomatic diagnosis for the first time to individuals at RVCL risk. The current literature about this topic has only been published for CADASIL, CARASIL and Fabry disease [6-8] but not for RVCL, in which only has been proposed [9].

Subjects and Methods

A *TREX1* gene mutation (c.703_704insG; p.V235Gfs*6) was previously identified in two siblings and one cousin with RVCL [5]. These related patients came from a village located in the State of Mexico, and mentioned that there were additional affected relatives over several generations. Considering the pattern of inheritance of RVCL, we invited to at-risk relatives who voluntarily wanted to participate in the study by completing a home visit.

Participants were studied based on three strategies: screening for *TREX1* mutation, health education, and genealogy study of the families involved. During the visit to the community, some relatives asked for a clinical evaluation and molecular diagnosis due to a common ancestor. They were informed that PD was an additional process, we accepted this request, but clarifying that the genetic results would be given at our institution after a pre-symptomatic evaluation. Thirty-eight additional samples of relatives were collected for molecular analysis to characterize the *TREX1* genotype of 4 generations in this genealogy.

It is important to note that no financial or material compensation was provided. Two neurologists evaluated all participants, and a well-structured clinical interview was done asking directly about any neurological symptom. Written informed consent was obtained from each subject after a complete description of the study, which was approved by the local ethics committee. After several interviews with various family members and with the help of a local historian, the genealogy of five generations of this family was reconstructed.

After the home visit, several participants requested their molecular results. Thus, based on previous experiences with genetic counselling and pre-symptomatic diagnosis (PD) of Huntington´s disease in the Department of Genetics at our institution, a group of PD was launched. International guidelines of the World Federation of Neurology [10] and specific guidelines for PD [11] were followed to apply PD to eleven individuals.

Results

Eleven relatives requested and were admitted for PD, including six men and five women with a mean age of 28 ± 6.8 years (range: 20 - 40). The average years of schooling were 14.3 ± 2.9 years (range: 9 - 17). At the time of testing, six participants had not a stable relationship, and the remaining five already had offspring and partner. After neuropsychological testing (to assess depressive symptoms, anxiety, memory problems, social networks, etc.) and psychiatric interview, only 8 out of 11 people were given the results, including six individuals who were positive for the mutation and two who were negative. The remaining three individuals with symptoms of depression and anxiety were judged to be unfit to receive their molecular results, and were referred for psychiatric attention. One of these last participants, after receiving the corresponding treatment and having improved from his depressive symptoms, came back to the hospital and requested his molecular result, which was positive. For the other two subjects, once the psychiatrist considers them to reapply, the outcome will be provided; however, until now, they have not come back. All participants with a positive result in the PD group were invited to open a file at our Institution for monitoring and attention, but only two accepted this proposal, the others have medical attention in different hospital centers; however, they still have the option of come back to our Institute at the moment they decide it. Eight months later of the mentioned PD, another asymptomatic relative visited us to request her result; but despite being scheduled for more than one appointment to be evaluated, she did not come back. Based on our experience, we followed a multistep procedure for genetic counselling and PD for RVCL in order to obtain minimal harmful consequences of genetic testing and a high psychological well-being after the PD process (Figure 1).

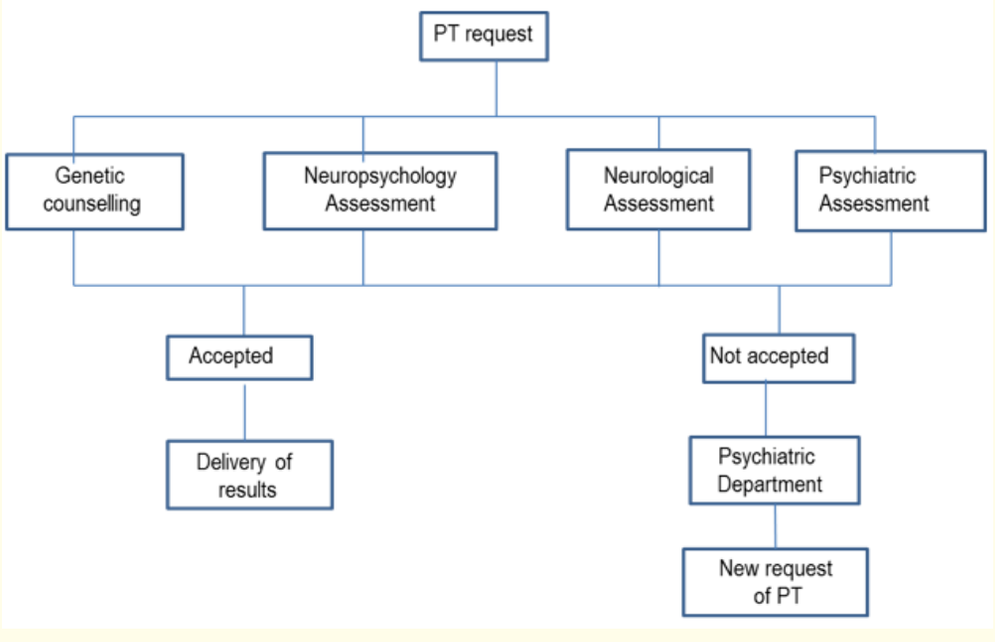

Figure 1: *Multistep procedure for genetic counselling and pre-symptomatic test for retinal vasculopathy with cerebral leukodystrophy.*

Discussion and Conclusion

This is the first report of PD in a large genealogy at high risk of RVCL. Genetic counselling is very important in this disorder since the mode of inheritance is autosomal dominant. This means that the progeny of an affected person has a 50% chance of inheriting the disease and developing it as an adult. In addition, the identification of a genetic cause is important to provide appropriate and timely counselling to the subject at risk, who in turn may plan reproductive, professional and personal aspects.

The study was offered to all at-risk subjects, but only eleven relatives applied for it. A few days post-PD session, two women married with men carrying the mutation, requested a molecular testing for their children. Since they were minors at that time, their results will be delivered until they become adults and request them in person. As in other inherited diseases, few people want to know their genetic status, mainly due to the lack of treatment. Despite this, we cannot limit the patient right for autonomous choice and the right of an informed decision based on this information.

Sometime later, a woman came to request her genetic result; however, she did not attend the scheduled appointments for her evaluation, implying that she did not really want to know her molecular result. This situation is also frequent in the PD program for Huntington's disease, mainly due to the lack of an effective treatment, that avoids or delays the onset of the disease. When the diagnosis is made in conditions for which it is possible to avoid or delay the onset and/or complications through preventive or intervention strategies, such as familial hypercholesterolemia or certain types of hereditary cancer, it is completely justified to perform it, inclusive in minors. But, in late-onset diseases where there are no preventive measures, the value of informing a person about their carrier status and the increased risk of developing the disease is debatable. In this case, the utility of genetic testing is not medical, is completely a personal decision, since it allows them to plan their future based on their genetic information. The reasons why a person decides to participate in a predictive diagnosis program are several, among them we can include: remove the uncertainty and that of their descendants, choose a profession, start or maintain a relationship and have offspring or not, among other. However, in RVCL, despite being a late-onset disease, it is likely that some changes in lifestyle may help to modify the evolution of the disease; thus the PD is fully justified, however, it is a personal decision, in which health personnel should not influence. Due to the late onset of RVCL, it is common that when the symptoms appear, most of the people already have offspring, so the decision to participate in a PD program gives their offspring the option of making informed health care and personal decisions.

Each child born to an individual with RVCL has a 50% chance of inheriting the pathogenic variant of *TREX1*, and this theoretical risk jumps to 75% for the offspring of couples where both parents are carriers when including the possibility of homozygous alleles. The presence of consanguinity in two marriages in this genealogy raises new ethical dilemma for geneticists. To date, there have been no reports of RVCL cases that include a homozygous mutant *TREX1* genotype.

RVCL is a rare disease, frequently misdiagnosed, and is caused by *TREX1* gene mutations which encodes the Three prime Repair Exonuclease 1 [12-14]. The clinical manifestations of RVCL begin in middle age, so the disease can be transmitted to the offspring before the patient has been diagnosed. Five frameshift RVCL causing mutations have been published [9]. In addition to this disease, different *TREX1* mutations have been associated with Aicardi-Goutières syndrome, chilblain lupus, Cree encephalitis, and other diseases of the immune system [12-14].

Due to RVCL is a multisystem illness; even familial cases can present clinical heterogeneity, making diagnosis and selection of a long-term treatment plan challenging. The confirmatory molecular diagnosis of RVCL is a non-invasiveness test with a high detection rate compared with MRI studies (where tumor-like lesions can be appreciated). Considering that RVCL is a severe multisystemic disease with a very poor prognosis, there is a need for closer cooperation between doctors of various specialties when caring for patients with RVCL.

As an extension of the present study we are planning to investigate the mutation in the entire population of the village, to further offer genetic counselling to all residents, particularly those of reproductive age. The asymptomatic carriers of the *TREX1* mutation (who will develop the disorder eventually) provide a model to study early stages of the disease with directed interventions, and the opportunity to identify modifier factors of RVCL, as well. The decision on whether to provide a diagnosis to asymptomatic carriers is complicated by medical, ethical and legal dilemmas.

Educational sessions are relevant for patients and their relatives since the phenotype of RVCL may be modified by other genetic or environment factors in addition to *TREX1* mutation. To include preventive lifestyle measures, we invited all participants to attend at least one RVCL-related health education session. In our experience, these sessions and PD can benefit all subjects at risk of the disease and help to minimize negative consequences of molecular testing.

Pre-symptomatic tests (PT) are tests that are performed to determine if a person will develop a hereditary disease before symptoms occur. This test is carried out at the request of the person at risk of suffering from a certain monogenic disease and wants to know if in the future he/she will develop the disease or not, even many years before any symptom could occur. PD is performed in the context of formal genetic counselling, and is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals.

This practice has generated changes in the exercise of traditional medicine since in this case it is not the doctor who requests the study, but the subject who wants to know if he/she will become ill in the future [15].

There are PT for two types of diseases: a) Those that have preventive and/or curative treatment and, b) Those in which still nothing can be done to prevent, delay or cure it; the latter are the ones that generate the most controversy since, on the one hand, if something cannot be done to help the person, why to do it? And on the other, you cannot deny the opportunity for a person to know her/his information and make important life decisions based on that knowledge. One of the most important aspects to consider when a person wishes to perform PT is the genetic counselling, which will provide all the relevant information that the subject requires regarding both the disease and what can or cannot be expected from the test.

Even before genetic testing was available, genetic counselling has played an important role in Genetic services for families affected by neurodegenerative conditions as a process that involves the exploration of the individual, family feelings, coping styles, and to inform about the reproductive options available [16]. It requires provision of enough time, space and resources to be developed.

The uncertainty surrounding the state of the mutation and the potential for transmission to the offspring, variability of age of onset, clinical expressiveness and penetrance, challenge effective practice and require advanced counselling skills.

The establishment of a respectful relationship between the multidisciplinary team that participates in the program and the applicant is essential for the successful completion of the DP.

Finally, it is also important to consider that once the *TREX1* pathogenic variant has been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic diagnosis for RVCL would be possible, which should not be done without including genetic counselling.

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Conflict of Interest

Authors declare no conflict of interest.

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