RUNNING A NEUROGENETIC CLINIC

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As a group neurogenetic conditions are not rare. We estimate that approximately 10% of patients with neurological conditions have a single mutated gene as the basis for their disease. Furthermore, when polygenic inheritance is considered (that is, the interplay between multiple genes and environment) a much larger proportion of neurological diseases are included.

WHY HAVE NEUROGENETIC CLINICS?

The explosion of molecular genetic information over the last 10 years has resulted in a large number of genes being discovered for single gene disorders. Since the majority of the thousands of genes expressed in humans are in the nervous system (central and peripheral nervous systems), it is perhaps unsurprising that mutations in many of the discovered genes cause neurological disease. At present neurogenetic clinics are concerned mainly with addressing important issues in patients with these single gene disorders. However, once more is understood about the polygenic disorders, they are likely to be seen increasingly in neurogenetic clinics.

The immediate benefit of these discoveries to patients is in DNA based diagnosis. This accuracy will facilitate reliable genetic counselling and presymptomatic testing if required. For some neurogenetic conditions screening for the development of complications is made much more efficient by accurate DNA based diagnosis. This will allow screening only of definite gene mutation carriers, as opposed to all individuals potentially at risk in a family.

Unfortunately, there is often a long delay between gene discovery and the availability of DNA based tests for patients with a given neurogenetic condition. The existence of neurogenetic clinics in each region in the UK, and the associated infrastructure links with regional clinical genetics, should allow a more rapid translation of gene discovery into clinical neurogenetic practice. Such translation into clinical practice is often most rapid when the clinical and research teams already collaborate and/or are in the same physical location.

Although treatments and treatment trials in neurogenetic diseases are in their infancy, this will almost certainly change in the future. There is increasing evidence that treatment responses will be determined by genotype. It is therefore important that patients with neurogenetic conditions achieve an accurate DNA based diagnosis wherever possible.

Accurately genotyped patients will then be in the best position to gain from therapeutic advances. Indeed, if, as we expect, therapies do become available for a number of neurogenetic conditions, there will be an increasing role for neurogenetic clinics in providing treatment.

WHO SHOULD RUN NEUROGENETIC CLINICS?

Running an efficient and effective neurogenetic clinic has to be a collaborative effort. The precise details are likely to vary from region to region in the UK. In our view, key contributors should include clinical neurologists, clinical geneticists, neurogenetic nurse specialists, and DNA clinical scientists. In addition there will often be close involvement of a range of other disciplines including physiotherapy, occupational therapy, speech therapy, and neuropsychiatry. Furthermore, we believe the neurogenetic clinic should play an active role in helping to train all the aforementioned staff. In our experience there is a particular need to increase the opportunities for neurology trainees to gain experience in neurogenetics. Ultimately there should be at least one neurologist with training in neurogenetics in each region in the UK. The previous model of neurologist as diagnostician and clinical geneticist as genetic counsellor often does not give the patient and family the best service.

FUNCTIONS OF THE NEUROGENETIC CLINIC

The neurogenetic clinic has a number of functions including clinical diagnosis, diagnostic genetic testing, presymptomatic genetic testing, prenatal diagnosis, genetic counselling, screening for complications, and the long term follow up of patients. Neurogenetic clinics should not be overbooked. New patient consultations usually take an hour while follow ups often take at least 30

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minutes. Other colleagues will often be present in the consultation, including the clinical geneticist and the neurogenetic clinical nurse specialist. Patients should be informed in advance about the multidisciplinary nature of the clinic, outlining the professionals who would normally be present. Patients should be given the option to be seen alone if they wish. On some occasions families will prefer to attend together. Continuity of care with the same doctor seeing the patient in clinic is the ideal. It is a very different experience to a routine neurology outpatients, and to try and prepare the patients and their families information sheets are sent in advance detailing the basic approach and what they are to expect from their appointment.

Clinical diagnosis and taking the family history

An accurate clinical diagnosis is the important starting point. Careful neurological evaluation by the clinical neurologist is essential. Appropriate neurological investigations are often needed. Practice varies, but in some clinics the neurologist will undertake this diagnostic phase and then in follow up clinics the clinical geneticist will attend to discuss in detail genetic testing and subsequent counselling.

Once the clinical phenotype is clearly categorised—for example, pure cerebellar ataxia, complicated cerebellar ataxia or demyelinating neuropathy—the first question to consider is whether the condition in question is genetic in origin? This question in itself may not always be easy to decide. The presence of a clear cut family history that obeys simple mendelian or mitochondrial rules of inheritance might make it easy to conclude the genetic origin of the condition. On the other hand, when late onset sporadic disorders are encountered it can sometimes be impossible to distinguish between genetic causes or non-genetic phenocopies (for example, late onset pure cerebellar ataxias). The absence of a family history is of course not proof of a non-genetic condition. The clinician must consider recessive or X linked inheritance, reduced penetrance, and variations in disease expression.

Taking a family history is not always straightforward. It is often a time consuming task and care should be taken to go into as much detail as possible about possible disease in other family members. If possible, other family members should be examined and efforts made to trace old records from other hospitals. Input from the neurogenetic nurse can be invaluable in constructing an accurate detailed pedigree. Pedigrees should be continually updated as new information comes to light. Often, the neurogenetic nurse specialist will undertake this important task.

Diagnostic genetic testing versus presymptomatic testing

It is important to emphasise the distinction between diagnostic genetic testing and presymptomatic genetic testing. Genetic diagnostic testing describes the situation in which a patient is offered a genetic test based on the symptoms and signs present—that is, the patient is symptomatic and the purpose of the test is to determine the cause of the current symptoms. For example, a Huntington disease (HD) genetic test may be offered to a patient exhibiting chorea. In this situation it remains important to explain the genetic nature of the test and that if positive the test result will have genetic implications for the rest of the family. It is our practice to obtain written consent for this type of genetic testing.

Presymptomatic genetic testing is an entirely different situation. The purpose of presymptomatic testing is to determine whether an at risk individual, who at the time of the test is asymptomatic, carries a mutant gene and (depending on the penetrance of the condition in question) will therefore develop the disease at some point in the future. The purpose of presymptomatic counselling, however, is to allow the patient to make the "best" decision for themselves having been fully informed. It is difficult to obtain an accurate assessment of this. One crude measure is to record adverse events post-result—for example, psychiatric problems, suicide, etc. Most experience in these issues come from the management of patients and families with HD. This is a fully penetrant autosomal dominant disease. At risk asymptomatic individuals may present to the neurogenetic clinic requesting to know their genetic status. Standard practice in this setting is to see the patient and discuss the issues around such presymptomatic testing on at least two separate occasions, usually separated by about three months. In some centres routine psychiatric assessment is part of the presymptomatic testing work up. Some at risk individuals find the uncertainty of not knowing their genetic status intolerable. In this group, after careful counselling, presymptomatic testing is undertaken. Presymptomatic HD testing has now been undertaken for several years worldwide since the HD gene was discovered. Most data indicate that carefully counselled presymptomatic testing has a useful role and is safe. Hopefully, this phase where we have the ability to diagnose serious neurogenetic diseases, but are not yet able to treat them, will be temporary. Once treatment for diseases like HD become available, it is likely that presymptomatic testing to identify gene carriers, in order to commence treatment, will become the norm.

Requests for presymptomatic testing in children are not infrequent and are entirely understandable. However, the generally acceptable practice for diseases with adult onset is that, if the at risk child is asymptomatic, presymptomatic testing is not offered until the individual concerned is able to make the decision for themselves. Usually this will be at the age of 18 years.

Prenatal genetic testing is increasingly available, usually by chorionic villous biopsy at 11–12 weeks gestation. Clearly, a DNA based diagnosis must already be achieved in the family and careful counselling is required. In particular an intervention, which is acceptable to the mother, should be agreed in advance of the testing, should the result be positive.

Selecting the correct genetic test

DNA testing is often time and resource intensive in terms of skilled DNA scientist time, equipment costs, and genetic laboratory running costs. Every care should therefore be taken to select genetic tests efficiently and carefully. Genetic test selection is based on the clinical diagnosis and on the results of additional investigations, and therefore it is extremely helpful to the lab to have access to as much phenotype data as possible as this will direct gene testing. It is important to give the patient a clear idea of the turn around time of a genetic test to try and minimise the anxiety of waiting for genetic test results.

Consent

It is our practice to obtain informed signed consent from all patients undergoing genetic testing. This applies to diagnostic as well as presymptomatic testing. We use a single DNA form for all types of genetic testing and also for simply storing DNA not to be tested. There are separate sections for consent to diagnostic testing, to presymptomatic testing, and to storage of DNA. We explain the nature of the test and outline the possible results.

For diagnostic testing the possible outcomes are:
(1) the test will confirm a particular genetic disease
(2) the test will exclude a given genetic disease, or
(3) that on some occasions the test may be inconclusive for technical reasons and may need to be repeated.

Furthermore, it is pointed out to the patient that if the test is positive there may be a risk of transmission which would subsequently be explained in detail. It is often also important to explain that the patient's condition may still be " genetic" even if that gene test is negative—that is, there may be other undiscovered genes that might cause the condition.

In presymptomatic tests the first two points are slightly different.

The options are: (1) the test is positive and this predicts that the patient will develop the disease at some point in the future; or (2) the test is negative and the patient will not develop the disease caused by this particular gene in the future. (This, of course, assumes that you have confirmed genetic proof of the diagnosis in another affected family member. This often requires collaboration with other genetic laboratories.)

Counselling

Genetic counselling aims to give patients as much information as possible about their condition and to explain the risks of transmission. This information should then enable the patient to come to his or her own conclusions about what they may or may not wish to do. It is essential that this information is given in a clear and understandable form. This takes time and patients must not be rushed but given every opportunity to ask questions. The clinical geneticist may take the lead in this part of the consultation. It is often very useful to reiterate the key points of the consultation in an information sheet or in a letter to the patient. Genetic counselling is a skill that can be taught. The neurogenetic clinic is the ideal setting for trainees to gain this experience.

Screening for complications

The neurogenetic clinic has an important role in considering the complications which may develop in some neurogenetic conditions. Common examples where screening may be needed include the neurocutaneous syndromes—for example, neurofibromatosis (NF), Von-Hippel Lindau syndrome (VHL). Various screening protocols have been suggested. For VHL a case can be made for presymptomatic genetic testing to identify those individuals truly at risk. This will rationalise the screening programme. VHL screening includes the following once every two years: magnetic resonance imaging (MRI) of the neuroaxis, abdominal imaging, retinal examination, and analysis of urinary catecholamines. There seems to be general agreement that in patients with NF routine extensive neuroaxis MRI scanning is not appropriate. Rather, regular clinical follow up is undertaken and imaging investigations are ordered based on clinical symptoms or signs.

Screening also encompasses facilitating the transmission of genetic information to other at risk family members who may not be the individuals actually attending the clinic. This needs to be handled sensitively. For example, in families with myotonic dystrophy, because of the phenomenon of anticipation, severely affected babies may be born to mothers with very little in the way of symptoms. It is therefore important that any females in myotonic dystrophy families should have access to this knowledge.

Planning each clinic

The varied nature of the situations which arise in the neurogenetic clinic, and the different professionals which collaborate, dictate that careful planning is essential. We hold a pre-clinic meeting the week before each clinic in which all cases attending are reviewed. It is particularly important to ensure genetic test results expected are in fact available! We regard such planning meetings as an essential part of any clinical neurogenetic service.

Whenever possible the results of genetic tests should be given to the patient by the doctor who counselled them. This is especially important for presymptomatic test results in serious conditions such as HD.

Who to follow up and why

Despite the current absence of curative treatments for all but a minority of neurogenetic conditions (for example, dopa responsive dystonia, isolated vitamin E deficiency) there is often a need to follow up patients. This may be for coordination of screening protocols, management of complications or, given the rarity of many of these conditions, simply as a source of specialist advice. Our practice is to offer follow up to patients with confirmed neurogenetic conditions often in collaboration with the referring centre. This may often be infrequent but our experience suggests this is the optimum arrangement for most patients.

NEUROGENETIC CLINICAL NURSE SPECIALIST

In our view it is not possible to run an effective neurogenetic clinic without a specialist nurse. Such specialist nurses have varied roles which compliment the service offered to patients by the rest of the team. The nurse will usually be present in the clinic and will in addition run their own separate consultation with patients to allow further explanation and counselling. A telephone advisory service, home visits, and liaison with community teams are other roles often provided by the neurogenetic nurse.

CONCLUSIONS

We have described our view on the basic requirements to run an effective neurogenetic clinic. We accept that views may vary. In particular we have encountered differences in opinion on the need for written consent for diagnostic testing, but it is our view that consent should be obtained in this setting.

It is important to emphasise the need for the collaboration of different colleagues. Effective infrastructure links between clinical neurologists, clinical geneticists, and the DNA scientific staff is crucial. Careful planning of each clinic to maximise efficiency is important.

It will be clear from the subsequent chapters in this supplement that there is now an enormous amount of genetic information which can be used to help patients with neurogenetic conditions. Indeed, there is now a case for subdividing neurogenetics. In some regions, for example, there are already separate clinics for muscle genetics and peripheral nerve genetics since these areas have become so large. Clearly, the starting point is to have an effective neurogenetic clinic in each region.

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