Panicos Shangaris, Module: Medical Genetics, IFWHG009

Discuss inherited disease using one or two named examples to demonstrate how risk assessment, screening, treatment and management of patients, carriers or family members is dependent upon the current understanding of the genetics of the disorder.

Introduction

Inherited disease is the disease, which is transmitted from generation to generation and is caused by gene and chromosomal abnormalities. There are five modes of inheritance in singe gene mutations: autosomal dominant, autosomal recessive, X-linked recessive, X-linked dominant, and Y-linked. Also, there are chromosomal abnormalities, which can be either numerical or structural. Complex disorders can be a mixture of both, not following a Mendelian or chromosomal pattern and also combining environmental factors (Harper 2009).

Diagnosis of an inherited disease can be challenging; certain steps need to be taken in order to assess if someone has the disease, is a carrier or is at risk of having children who might develop the disease.
We will discuss and explain the genetics and pathology of two disorders: familial amyloid polyneuropathy (FAP) and Friedreich's ataxia (FRDA). We will also investigate how these two disorders can be diagnosed and what a medical professional or a scientist need to consider when making the diagnosis. Counselling needs to be carefully delivered to the individual affected by the disease and also to the relevant family members. Research is also important in the diagnosis and understanding of the disease. Patients will be asked in some circumstances to take part in various clinical trials and research (Schulz et al. 2009).

Friedreich's Ataxia

Friedreich's ataxia (FRDA) is considered to be the most prevalent, in Europe, cerebellar ataxia in children and adults. An autosomal recessive disease caused by GAA triplet repeat expansion. This disease was firstly described by Nicolaus Friedreich in 1863(Filla, Cocozza, & De Michele 2001).
The prevalence is about 1 in 50 000 with a carrier frequency of 1%. It is present in Caucasians and absent in Chinese, Japanese and sub-Saharan populations (Filla, Cocozza, & De Michele 2001).

Ataxia and dysarthria are the main characteristics at around puberty; this is followed by sensory neuropathy, deep sensory impairment with the pyramidal tract getting involved (Durr 2002). Friedreich also reported the presence of other abnormalities like foot deformities, cardiac symptoms and scoliosis(Filla, Cocozza, & De Michele 2001). Around 10% of patients with FRDA develop diabetes(Pandolfo 2009).

Usually 10 to 15 years after the development of the disease, patients cannot walk, stand or sit without any help. Severe disease leads to wheelchair bounding for most of the patients within a few years. Dysphagia and dysarthia also develop.
Specific neuropathological features accompany the disease like loss of sensory fibre in the dorsal root ganglia and loss of sensation in the peripheral nerves. This disease leads to a reduction of life expectancy of 40 to 50 years (Schulz et al. 2009).
A GAA- trinucleotide repeat expansion located in the first intron of the FRDA gene on chromosome 9q13-21 is the main cause of the disease. This cloned gene gives a protein called FRATAXIN. While normal individuals have repeat expansions of 6 – 36, Friedreich's patients have an abnormally high number of 90-1300 repeats. The number of repeats is inversely proportional to the age of onset and directly related to the incidence of cardiomyopathy. Genetic studies in patients with late onset of the disease (LOFA) and no cardiomyopathy have a low expansion size in the range of 170-360 (See figure 1) (Di Donato, Gellera, & Mariotti 2001).

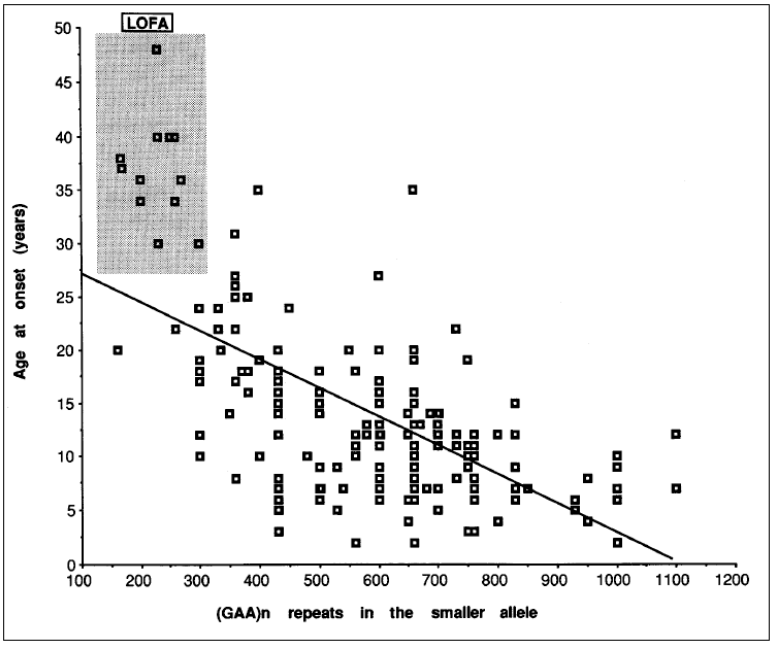

Figure 1, taken from (Di Donato, Gellera, & Mariotti 2001)

Typically patients are diagnosed with the disease from the clinical picture and genetical analysis of the patient's DNA for GAA repeats. PCR is usually used which offers quick and cheap results. As mentioned by Reddy et al (2007) in their case report it can sometimes lead to a false negative result.
Research on early diagnosis can be beneficial in providing and developing various therapies, coping strategies and eventually cure for this disease. Willis et al, (2008) suggest that the genetic problem does not lie in the coding sequence but in an intron. They demonstrated that the use of small molecule drugs could boost frataxin concentrations of the normal coding sequence in experimental animals.

Frataxin plays an important role in mitochondrial function. By reducing frataxin the cell becomes susceptible to oxidative stress, iron-sulfur clusters decrease and the mitochondria are Iron overloaded. Compounds like co-enzyme Q10 and mitoquinone, have been shown to reduce oxidative stress and some of them are in phase II trials in patients with Friedreich's ataxia(Hebert 2008).

Diagnosis

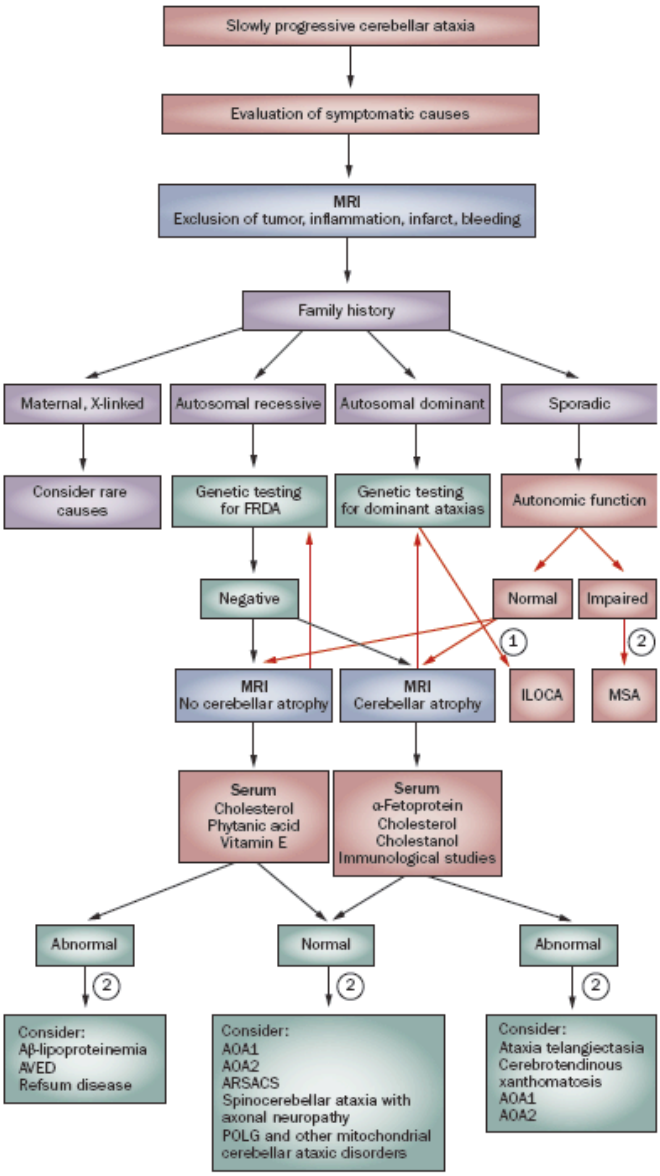

Figure 2. Diagnostic algorithm in patients with Friedrich's ataxia. (taken from (Schulz et al. 2009)

Initially the patient will have a history taking and a full neurological examination (See figure 2). Various neurological symptoms can then be picked up, like swallowing difficulties, tendon reflexes and visual disturbances. Loss of tendon reflexes in the lower limb is typical and there is frequent involvement of the Cranial nerves. PCR and southern blot techniques are used for the genetic testing of the patients. If both copies of the FRDA gene have GAA repeats, the disease exists. Some individuals might have the symptoms but carry a different mutation

with normal GAA repeat length and are still considered to have the disease. Sometimes a different disease can coexist in a carrier of FRDA, especially in high carrier populations.
It is not recommended to perform genetic testing on asymptomatic individuals, since the absence of a definite treatment will cause more unnecessary problems.
Parents of an affected child, or if both parents are carriers, can seek advice and can proceed with PGD (Prenatal Genetic diagnosis). Carrier testing is currently offered to spouses and relatives of an affected individual. If FRDA is confirmed, then more detailed clinical and neurological tests are performed such as electronystagmography, MRI, ECG, echocardiography, ophthalmological tests and also various haematological blood tests (Schulz et al. 2009).

Treatment

In every genetic disorder the use of a multidisciplinary team is essential since the disorder usually has a multisystem effect. Involvement of neurologists, cardiologists, endocrinologist and also orthopaedic surgeons is usually required.

Free radical generation and mitochondrial impairment causing cardiac and skeletal muscle symptoms can be improved by taking Coenzyme Q10 and Vitamin E. This was successfully demonstrated in an open label treatment (Lodi et al. 2001) and can be maintained for up to 4 years (Hart et al. 2005).
Ideberone, structurally similar to coenzyme Q10, has been used in a few studies, showing clearly the reduction of cardiac hypertrophy, and also the improvement in cardiac function. (Buyse et al. 2003; Hausse et al. 2002; Mariotti et al. 2003; Pineda et al. 2008; Ribai et al. 2007; Rustin et al. 1999)..
Histone deacetylase inhibitors are another potential way of treating Freidreich's ataxia. These have managed to recover frataxin expression in patients with FRDA and also in transgenic mice (Herman et al. 2006; Rai et al. 2008).
Early referral to a cardiologist is essential since cardiomyopathy can occur in patients with early onset of Freidreich's ataxia and can result to arrhythmias (Casazza & Morpurgo 1996).

Operative orthopaedic interventions, like spinal fusion are sometimes required to correct hyperkyphosis(Cady & Bobechko 1984; Labelle et al. 1986; Milbrandt, Kunes, & Karol 2008). Botox, splinting and orthopaedic shoes are beneficial in foot deformities. Walking aids and wheelchairs are required for the daily activities of these patients (Delatycki et al. 2005; Goulipian et al. 2008; Harris-Love et al. 2004).

Speech, language therapists and dieticians work closely together to manage ataxic dysarthria and dysphagia. The latter, sometimes requires the use of a nasogastric tube or gastrostomy feeding (Fox 2006; Yorkston et al. 1990; Yorkston, Smith, & Beukelman 1990).

Reports of social isolation and high levels of anxiety also exist and need special attention. Quality of life assessment needs to be performed regularly, as this can be influenced by the social and financial status of each patient (D' Ambrosio et al. 1987; Wilson et al. 2007).

Familial Amyloid Polyneuropathy

Familial amyloid polyneuropathy (FAP) is a lethal autosomal dominant condition, due to the deposition of amyloid fibrils. Valine is substituted by methionine at position 30 (Val30Met) of the transthyretin gene (TTR) (the most common type). Transthyretin is a transporter protein carrying thyroxine and retinol and also constituting the pre-albumin electrophoretic peak (Pareyson 2003). Amyloid composed of mutated TTR is deposited in autonomic, peripheral somatic nerves, heart and kidneys. It results in death within 10 years with variable age of onset (See Figure 3).

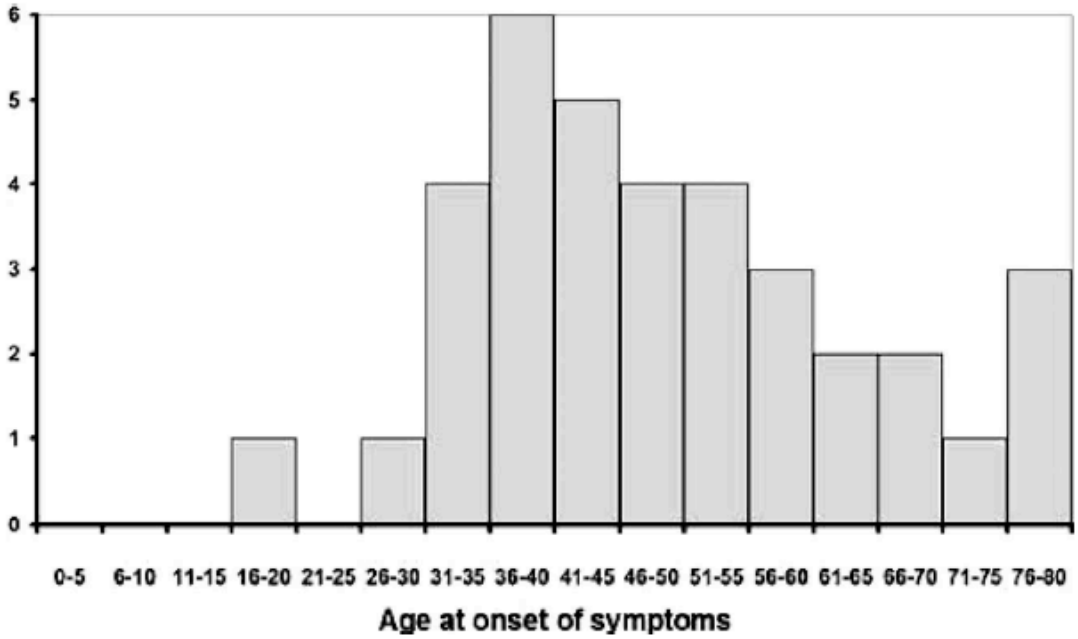

Figure 3. Taken from (Dardiotis et al. 2009a)

It is prevalent in a few countries such as Cyprus with a 38% penetrance, in Sweden with a 2% penetrance and Portugal with 80% penetrance. (Adams 2001; Dardiotis et al. 2009b; Dardiotis et al. 2009a). It was originally described by Andrade in Portugal, in 1952 (Dardiotis et al. 2009a; Said & Plante-Bordeneuve 2009). It can give rise to a cardiomyopathy with arrhythmia, congestive heart failure, acute death, vitreous opacities, seizures, hydrocephalus and also subarachnoid haemorrhage (Pareyson 2003). The majority of patients, initially, present with peripheral polyneuropathy, pain, sensory loss, motor disability and other non-specific symptoms as mentioned by Dardiotis et al. (2009a) (Monteiro, Freire, & Barroso 2004). Terminally ill patients with this disease are usually bedbound with flaccid quadriplegia, severe autonomic dysfunction, diarrhoea, vomiting and cardiac enlargement (Dardiotis et al. 2009a; Said & Plante-Bordeneuve 2009).

Molecular analysis of TTR mutations has made the diagnostic process easier. FAP diagnosis is difficult since a differential diagnosis of idiopathic chronic axonal neuropathy can be made, especially in the absence of any positive family history. Diagnosis is obvious if tissue amyloid deposits are demonstrated. Tissue from nerve, abdominal fat pad, rectal mucosa or skin can be biopsied. Examination

under slit lamp can reveal vitreous body opacities and electrocardiogram can be done to check for any obvious arrhythmias (Pareyson 2003).

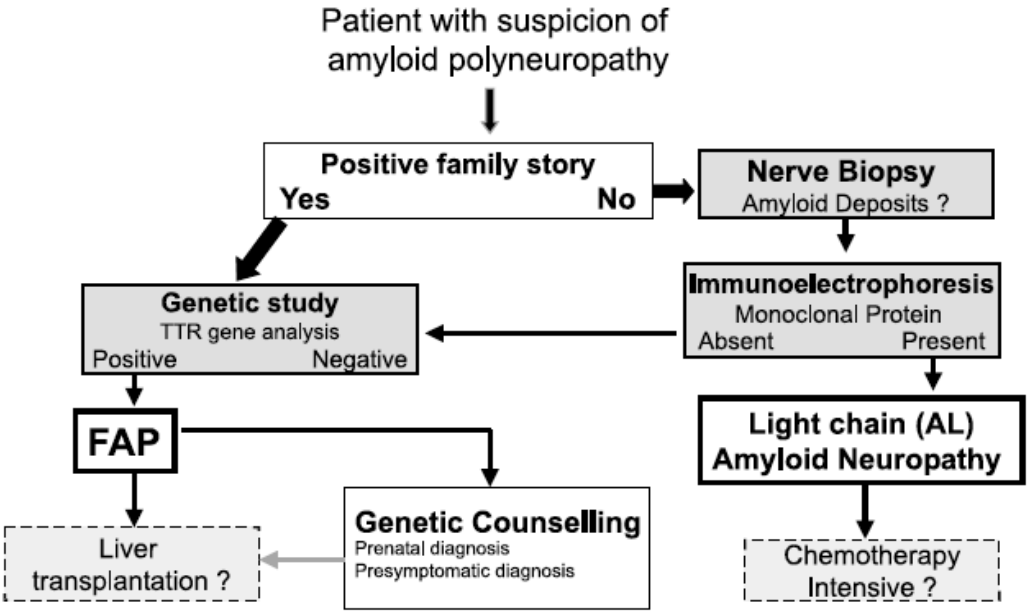

Figure 4 taken from (Adams 2001)

Diagnosis

The diagnosis of FAP is based on genetic studies. Patients with polyneuropathy symptoms and a positive family history undergo genetic study. The detection of a point mutation on the second exon of TTR gene usually confirms the diagnosis (Planté-Bordeneuve et al. 1998). Differential diagnoses need to be considered, like the FAP of the Finnish type or a non familial form, like Light chain (AL) amyloid neuropathy (see above, figure 4) (Adams et al. 1999). Prenatal Diagnosis is also possible as mentioned by Carvalho et al (2001)and Almeida et al (1990).

Treatment

Liver transplantation has been proven to be a successful method of treatment and had been the only available option until recently (Dardiotis 2009a; Pareyson 2003; Said & Plante-Bordeneuve 2009). Interestingly, Monteiro et al. (2004)mention a new way in liver transplantation called domino transplant where a Portuguese surgeon has done a sequential transplantation. A morphologically normal liver from an FAP patient was transplanted to a patient with liver metastasis where the FAP patient received a cadaveric liver. The procedure was accepted quickly in patients with a neoplastic disease but has raised ethical issues. Until December 2003 Portuguese surgeons performed a total of 151 domino transplantations(Monteiro, Freire, & Barroso 2004).

Symptomatic treatment is important in patients with FAP. The use again of a multidisciplinary team is essential. Burning pains can be treated with low doses

of clonazepam. High doses of dihydroergotamine can treat orthostatic hypotension. In cases with carpal tunnel syndrome the division of the flexor retinaculum is usually needed. Catheters can be successfully used in the treatment of urinary retention and prevention of kidney failure and infections (Rukavina et al. 1956).

Discussion

We have discussed the Genetics, diagnosis, and management of two genetic disorders with different features and symptoms.
Knowing the exact genetic mechanism, by which the disorders are caused, we can make plans for the management of patients, carriers and family members.
Treatment does not always exist, as in Freidreich's ataxia. Management of patients is based on the relief of symptoms and the quality of life of each patient. Even if treatment exists, like in FAP, it is not always straightforward. i.e. Finding a donor for Liver transplantation is difficult and it involves long waiting lists and the need for a cadaveric donor.
Couples might seek PGD if they find out that they are at a risk of transmitting a genetic disease to their children. Having no children, adopting or taking the chance with no confirmatory test in pregnancy might not be the perfect way for some couples (Harper 2009). Genetic counselling plays an important role before someone takes the step and proceeds to PGD.
The importance of a multidisciplinary team (MDT) was mentioned in the majority of the scientific papers. Genetic disease is usually a multisystem disorder. Patients with either FRDA or FAP need an MDT for the their management. Paediatricians, neurologists, genetic counsellors, endocrinologists, radiologists, occupational therapists, dieticians, pharmacists, nurses and others are essential team players.
Support for family members is very important and most of the times they also require genetic testing.
Finally, it should be noted that continuous advances in genetic research are fundamental as they provide a better understanding of diseases and can produce new ways of diagnosing, managing and treating patients.

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