



Achieving Integrated Services and Support for Families with Rare Genetic Disorders

Genetic Interest Group

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Preface: The Project

Although disorders caused by mutations in a single gene individually are mostly rare the number of conditions that result directly from a mutation in a specific gene is large. At least 5000 different conditions are listed and at least 1-2% of all births in the UK are of children with a significant degree of disability or an expectation of ill health that will potentially reduce the quality and quantity of life. Between a third and a half of childhood deaths are directly attributable to genetic disorders.

Genetic disorders have tended to be seen as a personal or family tragedy about which little can be done by way of a strategic response from the NHS to the needs of those affected or at risk. As a whole, caring for the consequences of genetic diseases and disorders represents a substantial commitment of NHS resources. Good sense, as well as good practice, would demand an integrated, strategic use of the skills, knowledge and opportunities available to ensure the best possible outcome for patients and their families and the optimum health gain for the NHS and for society as a whole.

The Genetic Interest Group (GIG) is the UK national alliance for individuals and families affected by genetic disorders. GIG was officially launched in 1989 by a group of voluntary organisations concerned with genetic disorders who saw the need to co-ordinate action on common issues. Primarily, these are to improve support and services for people affected by genetic disorders and to advance the knowledge and understanding of human genetics throughout the population. There are now over 100 groups in membership.

This report is the product of a pilot project funded by the NHS Executive. It identifies common experiences of services and support in families with a range of rare genetic disorders, in order to:

1. Identify appropriate directions for further research.
2. Increase awareness of the experience and needs of families.
3. Increase awareness of current good practice.

Four conditions were chosen for the study: tuberous sclerosis, neurofibromatosis, familial hypercholesterolaemia and haemochromatosis. All four are relatively rare disorders for generic clinicians in the NHS, but, compared with many other genetic disorders they are not that uncommon and contact with them will be a part of many doctors' professional practice. The experiences of those affected should have a resonance for many different disciplines involved in the provision of effective health and social care. The common thread linking them is the need for a number of different specialists to collaborate to provide the ongoing care that patients need. The nature of each condition and some details on the specific support group for affected individuals are given in section two of the report. The lessons to be learned from the experience of families with these disorders have implications for the ability of the NHS to respond to the needs of those with the four 'index' conditions and also for those with other rarer disorders which are genetic in origin and affect multiple systems in the body.

The report is based in part on interviews with clinicians and support workers for families. We are particularly grateful to Ann Hunt, Maggie Ponder, Julie Foxton and Janet Fernau for their

help and suggestions. The 20 case histories taken for section two of this report comprise the other indispensable part of the research undertaken for this project. We do not claim to have collected a perfectly balanced sample, but we do believe the cases presented highlight some of the important issues faced by patients requiring integrated services and support. We gratefully acknowledge the time given by the individuals and families who agreed to be interviewed. Each one presents the contributor's experiences from their own perspective as they described it to us. They are subjective, partisan and undeniably 'real' even if professionals involved might have different perspectives on what happened and why in each situation described.

1 Introduction

For many families the birth of a child affected by a rare genetic disorder comes out of the blue. Those to whom they look for advice and support at this time may be of limited assistance, given that they may have little or no knowledge of the condition and its likely impact on the affected child and the wider family. This is particularly true where the disorder may not be immediately obvious at birth but becomes evident soon after. Such is the case for two of the conditions studied in this report: tuberous sclerosis and neurofibromatosis.

For families in this situation a diagnosis is an essential first step in understanding what has happened, in coming to terms with this and in planning for the future. Getting an established diagnosis can also enable access to services provided by specialist clinics (often with financial support from voluntary groups) that will support the child with the disorder and the family in ways not easily managed by generalists, whether in primary care or at the local district hospital. Yet access to diagnosis and progressing beyond diagnosis into receipt of integrated services which reflect current best practice is not necessarily smooth or seamless. Some families move steadily and surely through the system, while others experience many delays and frustrations – all the way through from getting a diagnosis to receiving proper care.

Individuals with tuberous sclerosis and neurofibromatosis will usually exhibit their symptoms from an early age, but can expect to live into adulthood and may well experience a long life. Conversely, individuals with familial hypercholesterolaemia and haemochromatosis are unlikely to develop symptoms until they are well into their adult life, but may have that life cut short – however, if the condition is detected early or pre-symptomatically, action can be taken to delay, mitigate or even prevent symptoms from developing. This poses specific challenges for health service providers. But there are also parallels: diagnosis is often a problem, and its absence a cause of unnecessary complications and frustrations; multiple systems can be affected and ongoing care is needed. Integrating the services provided by a variety of different clinical, psychological educational and social care professionals so that families are able to benefit from systematic, consistent support is a challenge for health care planners. It is essential that this be taken up if those with rare conditions are to receive the services they need (to enable them) to gain and retain control over their lives. The NHS is committed to providing high quality care to all who might need it. Those with rare, complex disorders have a right to expect this at least as much as those with more common disorders.

1.1 Clinical Genetic Services

In the UK during the past 20 years, genetic services have evolved and changed more rapidly than many other specialities in medicine. Initially, paediatricians developed most medical genetic clinics; later other physicians, particularly those with experience of late-onset neurogenetic disorders, played a further role in evolving services. Today, an integration of clinical genetic, cytogenetic, molecular and biochemical teams all working together in one unit is favoured by the profession.

Ideally, the services are organised on a regional basis serving a population of between one and five million.¹

For some conditions, and for some purposes, patients require a narrowly defined service – for the diagnosis of a rare condition in a new-born child, or for genetic counselling prior to or during pregnancy, for example. In such cases, genetic services are the primary source of expertise for the patient, and will probably remain so in the future.

In other situations, genetic services may play a more limited diagnostic role or may contribute just one part of the care the patient or family needs. Such is the case with the four disorders used in this study. Many others could have been chosen, all with equal justification, because the provision of medical care requires a holistic view of the affected person and his or her family. This crosses many traditional boundaries between medical specialisms, leading government, professionals and patient support groups to examine the question of integrated care.

1.2 Integrated Care

The NHS Executive has made the development of 'pathways of care' a focus for health service planners in the years ahead. It wants Long Term Service Agreements to be based on 'pathways of care for different client groups or diseases, rather than on single elements within NHS Trusts.'²

In Scotland, a recent conference, 'Clinical Governance in Clinical Genetics', sought to apply some of this thinking to the field of clinical genetics. Organised by clinical geneticists with an input from public health specialists, it argued that 'experience in other areas of hospital practice has shown that Integrated Care Pathways provides a mechanism for the efficient capture of key data for audit purposes and for promoting the use of clinical guidelines into current practice.' From a study of the management of five disorders, Tuberous Sclerosis, Neurofibromatosis 1, Marfan Syndrome, Huntington's disease and Myotonic Dystrophy, it concluded that:

'Many genetic patients require multidisciplinary care and the precise nature and level of ongoing clinical genetic involvement varies across the centres often resulting in differing care for individuals, possibly even within a family. Use of accepted multidisciplinary guidelines common to each centre might reduce unnecessary variations in clinical practice and improve communication between professionals involved in patient care.'³

The documents produced by the 'Clinical Governance in Clinical Genetics' conference are useful in highlighting the issue of co-ordination. The limitation though is that the focus remains on clinical genetic services, rather than extending the focus to include broader issues of integrated care and service delivery in the NHS.

1.3 A Clinical Approach

For the patient affected by the types of disorder discussed in this report, the question of how care should be integrated or co-ordinated is closely related to the question of who should or is able to take a broad clinical perspective on the patient's needs.

Some clinical geneticists see this as being outside of their remit, which should, they believe, largely be focused on a diagnostic and family follow-up role. Putting the point strongly, one geneticist argued that clinical genetics is unable to play a broad co-ordinating role at present because (a) it isn't resourced to do so; (b) in some cases geneticists will not know enough about the normal variation in the functioning of a specific organ to clinically supervise an individual who might suffer organ deterioration for genetic reasons; and (c) other specialists might not appreciate being second-guessed in their field of expertise. However other clinical geneticists see themselves as playing a broader clinical role, perhaps in collaboration with specific disease or organ specialists – such as dermatologists, neurologists, psychiatrists, oncologists and others with relevant expertise.

The preponderance of non-geneticists involved in patient care implies that co-ordination must reach beyond clinical genetics. However the importance of understanding the origin of the disorder for the process of disease management, and the wider, familial consequences of genetic disorders would suggest a central role for genetic specialists. Section two of this report provides a snapshot of how things do, and sometimes don't, work in practice. In part based upon these studies, sections three and four outline some of the current models of patient care that might inform a more formalised protocol for integrated services. The Cochrane Collaboration structures evidence of clinical effectiveness hierarchically, with the meta-analysis of a series of double blind randomly controlled trials at the top, and shared professional judgements at the bottom rung of the ladder. Given the rarity of many single gene disorders it is difficult for health service planners to gather evidence of the kind advocated by Cochrane for the evaluation of effective practice. This makes the experience of families presented in this report all the more important for validating practice. Giving due weight and credibility to the experience and judgement of families and individuals affected by rare genetic disorders will be increasingly important for the NHS given the advent of N.I.C.E. and the growing need for services to be able to deliver evidence of health gain if they are to be funded.

Recommendations

Given the rarity of many single gene disorders it is difficult for health service planners to gather evidence with the necessary degree of scientific rigour to meet the criteria advocated by Cochrane for the evaluation of effective practice. This makes the experience of families presented in this report all the more important for validating practice. The NHS should ensure that it is able to recognise the value of user experience as a determinant of quality and effectiveness. (1.3)

2 Case Histories

2.1 Tuberos Sclerosis

Compared with many other single gene disorders, tuberous sclerosis (TS) is relatively common. A survey in the British Medical Journal documented that the two most recent estimates of its prevalence in the United Kingdom have been 3.7 per 100 000 in the West of Scotland, and 3.8 per 100 000 in Wessex.⁴ It was further suggested that this data failed to identify about half the prevalent cases, leading to an estimated population prevalence of 8-9 per 100 000. Another estimate is that it affects 1 in 10 000 new-borns.

Mutations in two distinct genes have been found to cause TS. In both cases it is a dominantly inherited genetic disorder, although 60-70% of cases are sporadic and represent new mutations. The genes are highly penetrant, but the severity of the symptoms can vary widely between individuals and within a family. In their normal functioning, the genes regulate cellular growth. Their abnormal functioning in patients with TS results in hamartomas or tumours in a variety of organs, most commonly the skin, the brain and the kidneys. When they develop in the latter two organs they are potentially life threatening, but otherwise TS does not carry the risk of a significantly shortened life span.

Clinically, the disorder presents with a range of physical and mental aspects. Facial angiofibromas rarely develop before the age of two, but affect approximately 85% of TS sufferers eventually. Hypomelanotic macules, also known as 'ash leaf' and depigmentation macules, are also a common sign, occurring in 80% of those affected. Many other markings and disorders may appear on the surface of the body. Calcified retinal hamartomas are also a distinctive feature of TS. Tuberous sclerosis is also a cause of some of the most intractable behavioural disorders in children. Both autism and hyperactivity can occur against a background of learning difficulties and uncontrollable epilepsy.⁵ The commonest early path to diagnosis is through epileptic seizures; in particular diagnosis follows infantile spasms, a form of generalised seizure seen in the first few months of life.

In a classic case of TS the diagnosis is never really in doubt, but when few signs are present, especially in young children who have yet to develop features of the disease, it can be difficult to be certain. Diagnostic criteria have been developed over the years, and continue to be refined. The imminent development and refinement of genetic diagnostic techniques will assist in this task.

When a diagnosis has been made, protocols also exist for the treatment and long-term management of the condition. In America, a Tuberous Sclerosis Consensus Conference, sponsored by the National Institutes of Health, developed recommendations for using diagnostic studies in three groups: (1) newly diagnosed patients with tuberous sclerosis, (2) established patients in order to detect late complications of tuberous sclerosis, and (3) potentially affected family members of children who have tuberous sclerosis.⁶ In the UK, the medical advisors to the Tuberous Sclerosis Association are currently developing clinical guidelines for the care of patients with TS. Once more, the development and refinement of genetic tests will aid clinicians – in this case by allowing them to make more

confident predictions about the likely course of the disease in affected individuals. In the Recommendations section of this report we make some suggestions of our own. But as the case studies indicate, problems of non-diagnosis, inadequate referral and poor social support need to be tackled alongside the refinement of models for prediction and monitoring for practitioners with expertise in TS.

The complexity of the physical and mental problems associated with TS has led to the development of a number of TS clinics across the UK. Typically, but not in all cases, these are based in the discipline of clinical genetics, with input from other specialists such as neurologists, psychiatrists and renal medicine specialists. The clinics usually meet monthly, and aim to work with other professionals who have responsibility for the patient. For example, this is how the Leeds TS clinic, which is headed by Professor R. F. Mueller, Consultant Clinical Geneticist, describes its work:

'The clinic offers advice in three problem areas of Tuberous Sclerosis: -

- (1) Assisting in the difficulties often met in the diagnosis of Tuberous Sclerosis.
- (2) Assisting in particular problem areas of management in Tuberous Sclerosis, such as behavioural difficulties and intractable epilepsy.
- (3) The investigation of family members for Genetic Counselling.

The clinic involves specialists from a variety of disciplines. The team includes paediatric and adult neurologists with special interests in intractable epilepsy, an ophthalmologist, radiologists for renal ultrasound and cranial CT scan and paediatric and adult cardiologists, amongst others. The clinic welcomes enquiries from medical, nursing and paramedical colleagues both in hospital and the community, caring for TS patients and their families. The role of the clinic is advisory and the plan is to work closely with the local medical staff involved with the patient and their family. The clinic is held monthly. To assist with the smooth running of the clinic, there is a clinic co-ordinator to whom all approaches should be made in the first instance so that appropriate appointments and arrangements for referrals can be made by GP's or consultants.'

A patient group, the Tuberous Sclerosis Association (TSA), was founded in 1977. All the TS clinics were set up with help from the TSA. Groups working to identify the genes involved in TS also received funds from the TSA. It runs Study Days for a variety of professionals working in fields relating to TS, and provides support to families affected by TS through a national family care officer and a network of regional representatives.

Tuberous Sclerosis Case 1

A mother and three children – two girls and a boy – affected by TS. The son is the most severely affected. The Mother was seen 17 years ago at a London hospital. But the information given was poor; she was told that the worst that could happen was that she would have a child with a harelip. This, together with the fact that the mother was only mildly affected, led to the family downplaying the risks. But when the eldest daughter was diagnosed as having TS, the mother determined to find out more and join the Tuberous Sclerosis Association. The mother has now lost her right kidney, and her left one has two cysts in it. The eldest daughter, currently 15 years old, is the worst affected of the two girls. The GP has described her behavioural problems as bordering on paranoia. She has had four unexplained blackouts. She tends to channel her behaviour through the mother, which increases the burden on her. But it is her son who is most severely affected and who has therefore had to be the focus of the mother's efforts: *"I had an option. I could try to sort my son out or I could try to sort my daughter out. What could I do?"*

Her son is now 11 years old. He has bad epilepsy, behavioural and social problems. He is now in residential schooling. All the way through, he and the family have faced the problem that professionals have failed to recognise the fact that his problems are at root caused by an organic disorder.

He had his first epileptic seizure aged four. These fits were going unrecognised at school. At six years old, his mother instigated an exclusion from school. However, social services said his family situation, not a medical disorder, was the problem. When the whole family visited a family psychologist, they were asked: "How can you expect your children to respect you if you don't respect yourself?" This attitude set the pattern. Professionals tended to reject the mother's references to TS as excuse making.

Aged nine he went to a mainstream school. He was very difficult to handle. He was teased about his epilepsy and tended to run away. At this point he was having up to 90 (epileptic) absences per day, and visiting the hospital once or twice a month in an attempt to control it. An intervention by the TS Association, which at last got educationalists and social workers to appreciate the organic origins of the problem, led to an admission to a school specialising in teaching children with epilepsy. Unfortunately, this has had the side effect of leading social services to appear to believe they could wash their hands of him during vacations. All this despite an assessment that stated that he needed respite care. Last summer he attended a play-scheme. But this was funded by the TSA, not social services. A consistent, ongoing programme has never been arranged. At the moment his seizures are less frequent, but more severe. His behavioural problems are reduced. This improvement is due in large part to the more structured environment provided by the new school.

Medical care has also been lacking. September 1998 was the first time he was seen by a paediatric neurologist. He is now due to see a specialist at a London hospital about growths and lesions on the brain. He is banned (!) from the local hospital, after he reacted badly to drugs he was given (about which the mother warned the hospital) and caused damage to two rooms.

Tuberous Sclerosis Case 2

A woman in her mid-20s. She has mild learning disabilities, and has been epileptic since the age of two. She also suffers from back and neck pain. The pain in her knees is sometimes so bad that she just collapses. Her mother had TS. She has a son aged two who also has TS.

She found out that she had TS when she was 13. She has had brain scans, but nothing else has been checked out. She is having problems with her legs at the moment, and an MRI scan has revealed that there is not much fluid in her spine, which could be a cause of the pain she is experiencing. She has never been to a TS clinic. Blood tests to check for liver disorders were clear, but such tests aren't decisive: *"I think I should have a full check-up"*, she says. She would like to be referred to a TS clinic, but her GP and the local psychiatrist who has been seeing her don't think this is necessary [it would mean an out of area referral]. She is trying to get around this with the help of the Tuberous Sclerosis Association. In her husband's view: *"she needs to get a proper referral, if only to properly understand that little can be done."*

Her son is under the care of a paediatrician. He is monitored every quarter at an out-reach clinic by a cardiologist and a neurologist from a London Hospital. In sum, he is receiving better care than is his mother.

Tuberous Sclerosis Case 3

An eight-year-old Jamaican boy, adopted at five months in Jamaica. He now lives with his adopting mother in the UK. He stays two nights a week and one weekend a month at a residential home.

When he was two and a half years old, he would keep pointing to his head. At three or four he would say "head", "head", "head aches". But because he has learning difficulties he found it difficult to communicate his feelings any better. He had a massive fit in 1994. His mother tried to convince everyone that there was a problem, but social services put his complaints and symptoms down to a behavioural disorder. They were, and still are, more interested in his 'identity' problems than his headaches. The surprising thing is that these responses have continued despite the fact that, after the fit in 1994, he had a CT scan at the local hospital, which led to a diagnosis of TS.

It wasn't until January 1998 that a specialist from a TS clinic saw him. On account of the fact that he was under a general anaesthetic at the time, a scan was not performed. But on looking into his eyes, no pressure build up was apparent. However, his symptoms continued to intensify during 1998. The doctors at the local hospital did not pass on the mother's concerns to the TS clinic, which has left her very bitter: *"He made it go on for another year. I was complaining, nothing was done. Are they naive or is it spite?"* When, at the end of the year, the mother kicked up a great fuss after his headaches got worse, the doctors at the local hospital took the attitude of "OK, to prove you're wrong, we'll do a scan." A different hospital performed a MRI scan in February 1999, and a large tumour was discovered. It proved impossible to remove the whole tumour surgically.

It is unclear what will happen now. A recent scan revealed that fluid is building up and that further operations may be needed.

His stomach has 'blown up' recently. The GP has refused to refer him to a TS clinic, so the mother has begun a complaints procedure to address the issue. Health issues still tend to be put down to his behavioural problems. Social services are now saying that they weren't aware of his headaches, but in the mother's opinion "*they are just covering their backs*". They also want to send him to a family care home for part of the time, to "give the residential home a break". His mother thinks this is just passing off the responsibility.

Tuberous Sclerosis Case 4

A man, aged 35, living in the South of England. He has six brothers and sisters. His condition is due to a spontaneous mutation. He is unable to read or write, but can hold a conversation. He lives at home within a caring family. He enjoys himself when he goes out with others.

Problems began when he was 18 months old. He was taken to a London hospital after developing infantile spasms and a bloated stomach. A diagnosis of polycystic kidney disease was made. Significant behavioural difficulties meant that he had practically no schooling. He was diagnosed as autistic. But because his kidneys did not give him any problems during his childhood, and it was felt that nothing could be done about his autism, he did not receive much medical care at this time. Despite facial blotches and bumps appearing ten years ago, a diagnosis of Tuberous Sclerosis was not made until things became critical more recently.

When he started passing blood with his urine six years ago he was admitted to the local hospital. Intermittent visits continued for the next two years. It was noted that he had high blood pressure, but no scans were taken of his kidneys. Then he suffered a severe turn: he turned pale and started vomiting. His mother asked his GP about possible kidney failure and what would happen, only to be told that it was already happening and to "just prepare yourself for the worst" as nothing could be done and the local specialists wouldn't see him, because, they said, he wouldn't be able to cope with dialysis. His family were having none of this. They threatened to expose the hospital's willingness to let someone die to the press, which forced the hospital to admit him for dialysis – just as he was collapsing with kidney failure. Transfer to another hospital and emergency surgery saved him. "*If we'd sat back and done nothing, he wouldn't be around now*", says his mother.

At the time of his kidney failure, epilepsy began. A testicle was removed after a cancerous growth was discovered. TS was also diagnosed. Since then treatment and monthly observation centred on Oxford has stabilised his condition. He had a kidney transplant two and a half years ago, which after some initial problems has taken. His fits are fairly infrequent (perhaps every few months or so). The facial markings caused by TS have also been taken care of.

His mother is very pleased with the care he has received recently: "*Tony is now a different person, excepting the difficulty he still has walking. It's a pity they can't all go to Oxford.*" But the anger and distress over his lack of treatment four and five years ago is felt very strongly to this day: "*What makes me so cross is that he could have been helped earlier – and he needn't have had kidney failure.*"

If it wasn't for the good work and support from the renal unit that saved his life, we would have sued the local hospital for the pain he suffered and the needless distress caused to the family."

Tuberous Sclerosis Case 5

An Asian male, 19 years old. His mother and father show no symptoms of TS. A twin sister and younger brother are not affected. Specific genetic investigation of the family has not been undertaken – this is the family's decision. His symptoms are quite severe, and he is now in residential care.

Epileptic fits began when he was 6 months old. Despite continuous care at a major London hospital, it was to take ten years for TS to be diagnosed. This followed the development of severe behavioural problems and a CT scan. Between the ages of ten and 16, he was under the joint supervision of a paediatrician and a neurologist. But since he was passed on to a new neurologist three years ago, his level of care has deteriorated in his father's view. It has been a constant battle to secure proper care and treatment. The neurologist and the GP batted him back and forth. The former said he had no intention of "wasting further NHS resources", by referring him for what the father understood to be quite necessary checks on his kidneys. Indeed, contrary to recommended guidelines he has never had a thorough scan of his kidneys. His GP threw him off his list of patients. In the father's view, "*the only helpful people have been the TSA.*"

In October 1998, he became very ill. He started vomiting, lost a stone in weight, suffered more frequent fits and became generally unsteady on his feet. A CT scan was performed, along with kidney- and liver-function tests. Up until this point he had never been referred to a TS clinic. Very concerned at this turn of events, the father pressed for a referral, which he got. The clinic has now arranged for an ultrasound scan of the kidneys to be done and has written to the neurologist promising to send him the latest draft of the clinical guidelines for the care of patients with TS once they are completed.

Recommendations

The experience of many families is of delayed or absent diagnosis, non-referral to sources of expert help and inadequate social support. Too often agencies and different clinical specialisms fail to communicate effectively (or even at all). Protocols, guidelines and other mechanisms to enable generic practitioners to gain access to expert advice promptly and effectively are needed (2.1).

2.2 Neurofibromatosis Type 1

In the nineteenth century, neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) were described as distinct entities. From the end of the nineteenth century until the 1970s they were commonly lumped together on account of overlapping phenotypic characteristics. But over the last two decades they have come once again to be described as distinct entities. Thanks to detailed clinical and molecular studies, they are recognised as distinct disorders caused by mutations in apparently unrelated genes. In the course of this project we

considered cases of NF1 only, which is by far the more common disorder of the two.

NF1, sometimes known as von Recklinghausen neurofibromatosis after the physician who first described the condition, is one of the most common genetic disorders, afflicting all ethnic groups, both sexes and all age groups. The birth incidence is around 1 in 2500, while the prevalence has been estimated at between 1 in 4000 and 1 in 5000.⁷ This lower figure is thought to be due to a combination of under ascertainment of mildly affected cases and disease related mortality.

NF1 is a dominantly inherited disorder caused by a mutation in a single gene, although around half the cases are new mutations. The penetrance is essentially 100% in individuals who have reached adulthood, but the severity of the condition is highly variable between individuals and within families – in some cases the parents of a severely affected child will not even have known that one of them had the condition. Neurofibromin is the protein product of the normally functioning gene whose mutated form, called *NF1*, is responsible for NF1. In patients with NF1 the loss of neurofibromin may lead to uncontrolled cell growth or tumour formation. As has already been mentioned, the disorder varies greatly in its severity, but on average it has been estimated that average life expectancy in adults is reduced by 15 years.⁸

The Hallmark feature of NF1 is the occurrence of benign tumours along peripheral nerves that may lead to cosmetic problems, overgrowth of limbs and symptoms of obstruction due to tumour bulk. Non-tumour manifestations include skeletal dysplasias, hypertension and learning disabilities. The incidence of the latter is estimated at between 30% and 60%. A range of sometimes-serious complications can develop. As our case studies indicate, non-diagnosis is a significant problem. But for those familiar with NF1, diagnosis is rarely a problem. Diagnostic criteria for NF1 were developed at a National Institutes of Health Consensus Conference on the issue in 1987. These are that the patient should have two or more of the following:

Six or more Café-au-lait spots

1.5cm or larger in postpubertal individuals

0.5cm or larger in prepubertal individuals

Two or more neurofibromas of any type

or

One or more plexiform neurofibroma

Freckling of armpits or groin

Optic glioma (tumour of the optic pathway)

Two or more Lisch nodules (benign iris hamartomas)

A distinctive bony lesion

Dysplasia of the sphenoid bone

Dysplasia or thinning of long bone cortex

A first-degree relative with NF1

Assessing the course of development of the condition in an individual patient is particularly difficult in neurofibromatosis. Some things are known. For example, in her 12 year follow-up study of Swedish adults with NF1, Zöller points out that:

‘among the clinical findings noted as diagnostic criteria for NF1, only that of numerous skin neurofibromas was significantly associated with increased mortality. Psychiatric illness and learning difficulties at school (remedial class attendance) did not contribute to reduced survival, nor did neurological defects in the form of impaired vision or hearing.’⁹ But on the whole, difficulties posed by the variability of the condition are compounded by the unpredictability of the emergence of often-serious complications.

There are some situations in which genetic diagnosis is useful, such as to confirm a diagnosis when the symptoms are very mild. Others may simply gain reassurance from a definitive genetic test. But in general genetic testing plays a limited role because it is unable to help clarify the aforementioned murky prognosis. Variations in the severity of the condition are marked within the same family, that is, among people who are carrying the same mutation. It should also be mentioned that a further limitation on the use of genetic diagnosis is the fact that it is technically difficult – and time-consuming – to perform due to the large size of the *NF1* gene and the number of different mutations involved.

The situation may change in the future: it is the hope of researchers in the field that a better understanding of the products of the *NF1* gene will lead to better management of the disease. Some also believe that if more long-term studies were done on the natural history of NF1, it might be found that in fact different NF1-causing mutations do tend to lead to a different disease pattern.¹⁰ However, at present, what evidence there is does not suggest this; all that is indicated is that certain other genes may play a role in modifying the likely course of the disease.

On the whole, there is a greater danger of new problems emerging during childhood and adolescence than in adulthood. Accordingly, the usual pattern of care is that children with NF1 are checked every six months or yearly for complications, while adults are seen by disease specialists for their major symptom(s) and have their blood pressure checked by their GP, but otherwise monitor themselves for possible complications. However, this is not a fixed pattern; in Manchester for example, the regional genetics service offers annual check-ups for adults. In the Themes and Recommendations sections we offer our views on the appropriateness of this approach.

The multi-system character of NF1 suggests that specialist clinics might be the most appropriate setting in which to monitor and treat NF1 patients. Some specialists in NF1 advocate this approach, and a number of such clinics exist or are coming into being in the UK. Once again, these issues are discussed in the Themes and Recommendations sections.

A patient support group, the Neurofibromatosis Association, which covers both NF1 and NF2, was formed in 1981, since when it has steadily expanded. Its focus is the network of family support workers it has established across the country. Ten are located in genetics departments, one in a neurology department. They are funded almost entirely by the charity. The service they provide is free and they have enough autonomy to be able to give independent advice in all types of settings, from health services to education and social services.¹¹

Neurofibromatosis Type 1 Case 1

A girl aged 10, living in Devon. She has two brothers, aged 19 and 16. The family has never seen a geneticist, but all the indications from family history are that the daughter's NF1 is due to a spontaneous mutation.

Problems became apparent when she was 12 weeks old. She was referred to an orthopaedic surgeon within the county for an examination of a bowleg (which was later to be diagnosed as a pseudarthrosis). He thought it might be rickets, but soon realised that it wasn't. No other symptoms were present at the time. Two months later Café-au-lait spots appeared. Soon after, neurofibromatosis was diagnosed. The next two years were a very stressful time for the family. The surgeon told them that she would need surgery on her leg, but he couldn't tell them when this would be done. When she was two and a half years old she was referred to a leading surgeon near London. Six months after that, the first of what would turn out to be several operations was performed. Her leg was broken then pinned with a metal pin the size of her tibia. She was in plaster for nine months. When this was removed she was able to get about fairly normally for her age. But a second operation when she was about five left her with one foot smaller than the other and turned inwards to the two o'clock position. By this point she was also aware of her limitations and her café-au-lait spots. She lost some of her chirpiness and the family felt 'knocked back'.

After an accident three years ago, it was discovered that she had hydrocephalus. A shunt was eventually fitted at a different hospital within the county. But this went badly. It became infected, and while in the hospital she contracted meningitis and peritonitis. This was the worst experience the family has had. The surgeon who fitted the shunt was away on holiday. He hadn't left instructions on how the care should be managed. Indeed, another surgeon had to step in to deal with complications, as the original surgeon's team were not monitoring her properly. Nor was anyone put in charge of communicating with the mother, who stayed with her daughter for much of the one-month period she was in the hospital. She wasn't even told about the infections at the time. The surgeon hasn't spoken to or seen the family since. The mother was so mad that she was thinking of suing. However, a strong letter from the daughter's paediatrician has helped to establish a structured regime of care.

"Our life is Jade because we have to take everything at her pace" says her mother. *"Touch wood she is going through a good patch now."* She has had a full-time classroom assistant all the time she's been in school. Initially, the assistance was just for mobility, but now she also requires some help academically as her work is slipping, probably on account of her hydrocephalus. The care is now divided between four teams: the surgeon near London who checks her leg once a year, a paediatrician who does an annual check up and generally looks after her, a team from the hospital that fitted the shunt, who perform six monthly check ups on her head and a local ophthalmologist for her astigmatism. The mother is full of praise for the paediatrician: *"He treats her as a whole person"*. When there are problems to sort out or reports to write for school she goes to him: *"He's like my right hand man"*.

Neurofibromatosis Type 1 Case 2

A girl, aged 8, living in the Merseyside area. The condition is due to a new mutation. She is mildly affected overall. Her mother, recently separated from her father, has an older son. The experience of dealing with her daughter has led to the mother becoming involved in the NF Association. *"Without the Association's knowledge"*, she says, *"I'd be tearing my hair out by now."*

At birth, breathing problems (unrelated to NF1) led to ongoing observations of the baby to check for brain damage. The paediatrician monitoring her noticed that she started to develop café-au-lait spots at six months of age. He realised that this might be neurofibromatosis, but didn't tell the mother straight away. At nine months she started to develop neurofibromas, at which point the paediatrician told the mother the news and said that the whole family should see a geneticist. *"Clinically I couldn't find fault with the paediatrician"*, says the mother, *"but his bedside manner was a nightmare. He just gave us the diagnosis, leaving it to our GP to explain everything."* In a panic, worried about tumours and whether they might be malignant, among other things, she phoned the local regional genetics service as well as medical friends.

The mother has not had a *"great deal of faith in local medical specialists"* ever since a medical advisor to the NF Association told the mother that a different local paediatrician had probably been wrong in suggesting that a swelling on her daughter's back was not a plexiform fibroma. The mother is not aware of anyone in the area specialist in NF1, apart from one clinical geneticist. This is not to say that the local genetics service is uninterested: *"the genetics staff in the area are great, but they don't have the resources for regular consultations. I feel extremely envious of the Manchester set-up where people can go back every year for a general check-up."* Given her own knowledge of the issue, the mother plays a crucial role in monitoring her daughter for any complications. To date, the symptoms have been quite mild: her daughter has one large plexiform fibroma, many small neurofibromas and lots of café-au-lait spots. Intellectually she is above average in her class, but she does have some motor-skill problems and, perhaps linked to this, a few problems mixing with other children.

A consultant paediatrician at the local hospital has responsibility for co-ordinating care at the moment. But there does not seem to be provision to monitor people who are affected as they move into adulthood. The mother is worried about accessing the relevant services at this point: *"there probably are some experts, but the problem's finding them and getting access to them."*

Neurofibromatosis Type 1 Case 3

A married couple with two children; a son aged 7 and a daughter aged 4, living in East Anglia. The mother and son are mildly affected with NF1. The daughter is more severely affected.

The mother had fibromas removed 15 years ago, but the condition was not diagnosed at the time. It was only when she was pregnant with her son that a diagnosis was made. She didn't pursue the issue at the time, but six months later, after reading an article on neurofibromatosis in the press, she saw her GP and

an appointment with a geneticist was arranged in Leeds, where the family was living at the time. The geneticist explained the risks of certain possibilities, but as both the mother and son were mildly affected, they didn't worry too much: *"the geneticist never explained how seriously affected a future child could be. It was very textbook in style. A 65% chance of learning disability was the only thing that caused concern."*

The mother was monitored a little, but was told not to worry too much. When her son was two the family moved from Leeds to East Anglia. By now he was hyperactive. This brought the family into contact with the NF Association. At this point another baby was on the way. Looking back on it, the view of the parents is that they *"probably would have gone ahead with the second pregnancy regardless"*, but they really should have been made aware that they *"could have had a child with severe difficulties."* They feel that a proper diagnosis should have been made 15 years ago when the mother's fibromas were first removed, and at the very least that their initial consultation with a geneticist should have been more informative. *"We are lucky in having, for the moment, two children who are mildly affected. Our decision to have children was easy because we were ignorant. In the future perhaps IVF will give people the choice to avoid the birth of a child with a condition if that is their wish."*

The care since the second child was born has been good. The local hospital was very honest in saying that the condition was probably beyond them as far as treatment went. This led to a swift referral to Oxford. The family's own knowledge, gained through working with the patient support group, helped here as they were able to demonstrate more knowledge of the condition than many at the local hospital. The daughter has been to Oxford four times now: initially once every six months, then once a year. She has been monitored more than the son has due to cranial-facial problems. There have been few problems at school: the teachers are aware of the problems that might arise, and NF Association family support workers are available to help as well if the need arises. All in all, they feel fortunate that they have had the attention that they have: *"some other families get a much worse deal."*

Neurofibromatosis Type 1 Case 4

Father, daughter (age 16) and son (age 5) affected. One more daughter (age 12) not affected. The father was not diagnosed until his daughter was born with the condition. He has never had an investigation to determine whether his is a spontaneous mutation or an inherited condition – his mother died early and his father will not discuss it. His brothers are not affected. He is mildly affected – a few *"lumps, bumps and patches"* and mild dyslexia. This has not prevented him from developing a career, but the absence of a diagnosis for a long time did lead to family tensions and social difficulties. He does not seek or receive medical care at the moment. The son is also mildly affected – café-au-lait markings and one plexiform fibroma. He is a little slow in his writing, but not too much. He is having six-monthly check-ups under the care of a paediatrician.

The daughter is not significantly affected mentally, and many of the other usual symptoms are quite slight. However, she has had to have a lower leg removed recently after a long struggle. She

was not diagnosed as having NF1 until she was about five or six years old. Pioneering leg-lengthening surgery was tried for many years to tackle her pseudarthrosis, but ultimately without success. Throughout this period she received very little support from the medical profession. Her GP didn't like to visit. Little advice was given on how to balance the range of medicines being administered. The consultant overseeing the series of operations on the leg gave the family very little information on the likely duration and severity of the treatment that he was administering. When the family moved house about nine years ago, they were fortunate to get a new GP who has been very helpful, both in terms of making home visits and in helping with letters to benefits agencies and the school. And after seeking a second opinion from another consultant, the family feels that the medical side of things is now being handled better as a whole, although it still falls on the family to co-ordinate medical services to a large extent as the local paediatrician seems to have only a limited knowledge of NF1 and the daughter's history. There is also a concern about what will happen as the daughter moves into services for adults.

To the frustrations on the medical side must be added the ongoing struggles the mother is having with benefits, housing, and educational agencies, all of which has taken its toll: *"we've had to battle, going up to the top person every time. It's a full time job, and that's not including the time spent caring for my daughter. Other relationships within the family have suffered. Everything is based at home – in the two years since the surgery we've been pretty much house-bound."*

Neurofibromatosis Type 1 Case 5

A man aged 21, living in the North of England. His neurofibromatosis, which is caused by a new mutation, was not diagnosed until he was 15 – or at least his family were not told until then. In his mother's view *"it is unbelievable really, especially since he had been in and out of hospital so often. He's always had lumps and bumps on his body. Only when he was seeing a surgeon for clubfoot did it come out – he showed him his spine and blotches and the surgeon diagnosed it on the spot. I don't know whether all the different doctors thought we knew so didn't say anything or whether it was just a fluke that no-one spotted it"*.

Born one month premature, he was very ill at birth. His breathing was poor and he suffered from a number of different infections. He was also born with his right foot twisted around 180 degrees. This was manipulated and put in splints straight away. After spending some time in an incubator, he was sent home after a month; his family were told that he might recover, or he might die. Either way the hospital could not do any more. He pulled through his post-birth illnesses, but the twisted foot proved to be the first of many problems that it is now known are due to NF1. Besides his foot and ankle, which have required four or five corrective operations, his symptoms have included hyperactivity, problems of co-ordination, many fibromas and café-au-lait spots, present since birth, and problems with his sight. He also suffers from backache due to scoliosis, and had to have surgery to drop one of his testicles. Most likely unrelated to NF1, he also has a cleft palate.

Even when they were told what the problem was, no one sat the

family down and explained the situation. They had to find out information for themselves at first and then from the Neurofibromatosis Association. The family GP is now performing regular check-ups, but the worry is that something more is needed. Overall, there is a strong feeling that more backup should be provided.

Not knowing what the problem was, and therefore not having anyone else to turn to who had been through a similar experience, left the family feeling generally isolated. But in particular it was schooling that placed the biggest stress on the family. *“The only way I can describe it is that it was a nightmare”,* says his mother. *“He was always put down as a naughty boy.”* Things did not improve that much when they got a diagnosis: *“I know NF1 is not widely known about, but the hardest thing was convincing the teachers at school; one pretty much laughed in our faces as he thought we were making excuses.”*

2.3 Familial Hypercholesterolaemia

It has been estimated that familial hypercholesterolaemia (FH) is responsible for 5% of cases of coronary artery disease before the age of 55 in the UK. It is a disorder of lipoprotein metabolism, and is characterised by raised cholesterol in general and raised low-density lipoprotein (LDL) cholesterol in particular. For a given age and sex, the LDL of an individual with FH will, on average, be twice the normal level. The raised risk of coronary artery disease results directly from the raised LDL level.

It is an autosomal dominant genetic disorder with an estimated incidence of 1 in 500 for the heterozygous state in the UK population – that is, 110 000 people in the UK are thought to be FH heterozygotes.¹² The disorder is caused by mutations in the LDL receptor gene, which lead to a lack of functional LDL receptors on the cell surface, and hence an excess of LDL cholesterol in the blood. Worldwide, 500 different mutations in the gene have been identified. This wide spectrum at the DNA level is reflected in the considerable phenotypic variation of the mutant receptors.

The different mutations in the LDL receptor gene, along with other genetic and environmental factors, contribute to variations in the risk of coronary artery disease among FH patients. The role of the different elements is not yet fully worked out. But what is known is that on average, being heterozygous for FH significantly raises the risk of heart disease. According to the World Health Organisation, surveys show that, left untreated, the risk of a male with heterozygous FH experiencing a myocardial infarction is 50% by the age of 50 and 85% by the age of 60. Corresponding risks for women are 15% and 50%.

Treatment for FH will typically be monitored by a lipid clinic, of which there are 156 in the UK. The basic aim is to reduce LDL cholesterol. Diet and other lifestyle advice plays its part, but it is a characteristic feature of FH that drug treatments are usually needed. Typically, these can achieve a 25–30% reduction in LDL levels, with a corresponding one-third reduction in heart attack rates and a 40% reduction in related deaths. A recent study, by the Scientific Steering Committee on behalf of the Simon Broome Register Group, has broken down the relative increase

in risk of a fatal coronary event that remains, despite treatment, for FH heterozygotes compared with the normal population in the UK. It found that for younger adults with FH, their risk was increased 125-fold if they were female and 48-fold if they were male (facts which indicate the seriousness of FH in part, but also the good health of unaffected people of that age). In the oldest age group, women had their risk increased by a much lower amount, 2.6 times, while for men there was no differential at all. Reassuringly, the study also found that non-coronary mortality was not increased at any age by therapy for FH.¹³

The criteria generally used for diagnosis of FH are that a patient should satisfy the first of the following four conditions plus at least one of the others:¹⁴

- 1 Cholesterol levels above 6.7 mmol/l with LDL above 4.0 mmol/l in a child (under 16 years old), or above 7.5 mmol/l with LDL above 4.9 mmol/l in an adult (16 years and older), with a total triglyceride of not more than 2 mmol/l.
- 2 A family history of myocardial infarction below 50 years of age in at least one first- or second-degree relative.
- 3 Tendon xanthomas, or family history of such xanthomas in at least one first- or second-degree relative.
- 4 Cholesterol levels above 7.5 mmol/l in at least one first- or second-degree relative.

Genetic diagnosis may be used to supplement this clinical diagnosis. It may also be used as a primary diagnostic tool in other family members; that is, once the mutation is known, although a clinical diagnosis will also usually be made as well.

As our case studies show, in practice the tragedy is that diagnosis often follows, rather than precedes, the symptomatic development of coronary artery disease. Sometimes it only comes many years after the development of disease. 30% of patients will not have an afterwards, for they will be dead. For the rest, although diagnosis will help secondary prevention, the result is likely to be a worse prognosis than if detection had come earlier, before the primary episode.

Professionals and patient groups working in the field therefore focus on means of improving primary prevention. Geneticist Steve Humphries believes that FH meets all the criteria set out by Wilson and Junger before screening for a disorder should be undertaken. He argues that testing of family members should begin in the near future. The Family Heart Association (FHA), which represents patients with FH, also emphasises the importance of following up family members. Another focus for the FHA is on improving understanding within the primary healthcare team of the need for referral and specific, often drug-based, treatments for people whose cholesterol is significantly raised for familial reasons. To further both of these aims it has developed training packages for healthcare workers and has recently mailed every GP in the UK with information about FH.

Familial Hypercholesterolaemia Case 1

A man in his 60s, living in Lancashire.

The patient suffered acute angina and then a heart attack in 1990, which left him in intensive care for 3 or 4 days, followed by 6 days on a hospital ward. He had to request a cholesterol test, after a friend suggested it. His cholesterol level was 8.6. Dietary measures and drugs have brought that down to 5.5. His father had two heart attacks. His mother had a mild heart attack. His sister has a very high cholesterol level (Approx. 11) and has recently had a triple bypass operation. No genetic tests have been performed. He has three daughters. The two youngest have had their cholesterol levels measured as unusually high. The oldest has chosen not to be tested – he thinks she takes too much of a “*what will be will be*” attitude.

His GP now has the basics under control. However, while “*the practice nurses have been informative*”, he feels that information is not fed back to him by the GP; it was via the Family Heart Association rather than his GP that he got in touch with a lipid nurse. “*There is work pressure on GPs, but they could communicate more*”. He also finds it a problem that he is sometimes seen by a different GP in the practice, who might not be so well informed about FH.

Familial Hypercholesterolaemia Case 2

A 40 year old man, living in Scotland.

Four or five years ago, his step mother called him to say that his father, with whom he was out of touch, had been in hospital with heart trouble and that he should get his cholesterol levels checked out. His paternal uncle had died of a heart attack. A check-up by the GP showed a cholesterol level of 6.8. He was told not to worry, but to watch what he ate.

In February 1999 he experienced angina. He saw a different GP this time. Blood tests showed the total cholesterol level to be 6.4. But this time the new GP picked up that his triglycerides were off the scale. He was referred to a cardiologist. An angiogram revealed that one artery is fully blocked, another half blocked. A double, perhaps triple, heart bypass operation is to be performed at the end of 1999.

When he looked at the blood results, the cardiologist said: “*ah, I think this is familial*” after he saw that the LDL levels were raised. But that was about all the patient learnt from the cardiologist about the origins of the problem. He wasn’t given a chance to discuss the issues with the cardiologist. Instead he was left hanging for 6 weeks until a referral to a lipid clinic took place. The referral to the lipid clinic has led to a new dietary regime and plans to visit the regional genetics service to fully investigate the genetic and family aspects of the situation.

It was fortunate that the genetic and familial aspects were picked up this time around, because it was the patient, not the GP, who brought the blood results to the attention of the cardiologist. Sadly, the patient has found out that the same information was contained on the blood test results of five years ago. The printout said: ‘trig high’ and broke down his cholesterol results into LDL and HDL levels. “*Five years ago this should have been picked up. I’m not saying I wouldn’t be in this position now, but I could have taken preventative measures*

earlier.” Looking to the future, his priority now is to get his children checked out if the genetic investigation suggests it is needed.

Familial Hypercholesterolaemia Case 3

A Woman, living in Southern England.

Visual manifestations of the disorder led to a chance diagnosis in 1982 by a physician while the patient was having a general check-up performed privately. Initially private and then NHS care based around a diabetic clinic was soon established. Unluckily, both the patient’s children were diagnosed as having FH. On the positive side, the health care at all levels was excellent, with the patient’s own GP becoming very interested.

The long-term nature of the condition and her membership of the Family Heart Association has led to the patient becoming interested and informed about FH. It came as a shock therefore that when she moved to a new area some time ago, everything stopped. Despite the patient’s own concern about a possible link between muscle pains, a new medication and FH, no referral has been arranged to see a consultant. She is even having to ask for blood tests to be done, and is then not given feedback on the breakdown of the results: “*I like to know my numbers; they are my numbers after all.*” Her 17-year-old son is taking medication but there is no monitoring of his cholesterol levels or his liver function. Overall she feels that she has “*slipped out of the system*” and is “*not being taken seriously.*”

Familial Hypercholesterolaemia Case 4

A man in his late 60s, Living in London

A specialist in familial hypercholesterolaemia made a diagnosis in 1990. This was five years after the beginning of a series of “*cardiac adventures*” that have continued to this day. “*I lucked out by being referred*”, says the patient.

The history runs as follows. The first bypass operation was performed in 1985. Angioplasty followed in 1987. In 1990 the patient suffered a serious cardiac episode. Feeling uneasy, he called an ambulance. On the way to the hospital he experienced cardiac arrest (ventricular fibrillation). This left him unconscious for 48 hours, and had the effect of leaving a permanent mental blackout of the preceding 48-hour period; in all a full 96-hour period was lost. A second heart bypass operation was performed in 1995. In August of that year an aneurysm was somewhat fortuitously detected and removed. Following palpitations and atrial fibrillation while on holiday soon afterwards, he returned to the UK and the hospital which had performed surgery before. An angiogram showed no cause for alarm, but while celebrating his discharge with “*a little too much champagne*”, he felt uneasy and returned to the hospital’s A and E department. While there he went into ventricular fibrillation again. “*I suspect that the hospital is very good at plumbing, but less good at electrics. I should have been, but wasn’t, warned that two bypasses had left my heart electrically hypersensitive and that I should go very easy on alcohol and caffeine.*” A ventricular defibrillator was then fitted by another hospital. In late 1998 he suffered a transient ischaemic heart attack.

The diagnosis of familial hypercholesterolaemia was made in 1990 after measurements taken during the earlier surgery led his GP to refer him to a metabolic clinic in a hospital. Before this happened, he was independently referred by a different hospital following the severe cardiac episode of that year. He was seen in August and put on a drug regime that has reduced his LDL level to 3.4. He is still being monitored; the aim is to get his LDL levels below 2.5. The feeling of having “*crashed an aircraft into a mountain not once but twice and walked away unscathed*” has left him with an accentuated sense of the highs and lows, and above all a desire to get on with life.

Familial Hypercholesterolaemia Case 5

A family with three children aged five, 11 and 13, living in the South West of England.

The husband died three years ago aged 37 from a heart attack while playing five-a-side football. He had visible symptoms of FH – corneal arcuses, and his father had also died of a heart attack, aged 47. Tests on the children have revealed that the 13-year-old has normal cholesterol levels, the five-year-old is borderline for raised cholesterol; total cholesterol 5.5 but LDL higher than it should be, while the 11-year-old has a high total cholesterol level of 9.8.

The husband’s GP died recently, which has made it difficult to trace the history of his treatment in detail, but what is clear is that while a diagnosis of familial heart disease was made when he was 17, the GP never explained the seriousness of the situation, nor dealt with the symptoms as vigorously as he could have. Despite a persistently high LDL level (approx. 12) a referral to a lipid clinic was never arranged and the hereditary nature of FH was never explained before the couple had children. Sadly, when the husband visited the doctors a week before his death complaining of chest pains and a general ill health, he was given indigestion tablets. It was only after the husband’s death that the family found out about the Family Heart Association – via a friend rather than the NHS.

“I know hindsight is a wonderful thing, but I feel bitter and cross”, says his wife. “37 is no age at which to die. He could have had better care. I’m determined now to make sure than my children, especially the 11-year-old, gets to see anyone who can help. Thankfully my GP, although he has admitted he doesn’t know much about it, has said he will push the issue.”

2.4 Haemochromatosis

Haemochromatosis was first recognised more than a century ago as a triad of symptoms – diabetes, skin bronzing and cirrhosis – associated with hepatic iron overload. It is a late-onset recessive genetic condition. The heterozygous state is very common in the Western world – one in ten of the population is thought to be a carrier. This leads to an estimate of 1 in 400 for the homozygous state. However, not all homozygotes develop significant clinical symptoms. The extent to which this is due to less than 100% penetrance and the extent to which this is due to variable expression is not fully known. But estimates of the burden of the disease have been made. In their study, Powell et al argue that ‘at least 50% of male and 25% of female persons

homozygous for haemochromatosis are likely to develop potentially life-threatening complications of the disease, especially in countries with high dietary intake of iron.’¹⁵ This amounts to a significant disease burden at the population level.

Iron is essential to normal bodily functioning. We absorb small amounts from food and lose a similar amount each day largely through cell loss in the gastrointestinal tract. However, the body has no way of excreting more iron and if an abnormally large amount is absorbed it accumulates in the body and in excess may be harmful. Haemochromatosis is the most common form of primary iron overload disease. It expresses itself as a tendency to absorb excess iron from the gastrointestinal tract. The earliest manifestation of the disease is a raised saturation of a protein in the blood called transferrin, which binds to iron and shuttles it around the body. Elevated levels of serum ferritin in the blood usually follow this, which is a sign that the body is beginning to overload iron. The excess iron is deposited in many bodily organs causing damage that can lead to heart and liver problems, insulin-dependent diabetes, arthritis, infertility in women and impotence in men.

It is now understood that the classical symptoms of the bronzed patient are in fact advanced manifestations of the underlying disease process. More typically, an individual in their 30s or 40s, more likely a male at this age, but not exclusively so, will present complaining of fatigue and arthropathy, perhaps accompanied by abdominal pains and impotence.¹⁶ If treatment is initiated at this point, before diabetes or cirrhosis develops, the arthropathy may well develop into arthritis still, but other serious complications should be avoided and the patient should enjoy a normal life expectancy.

Clinical diagnosis is based on tests for raised levels of transferrin saturation. If tests on two samples both register above 55% for men or 50% for women, it is very likely that the individual has haemochromatosis. Raised iron load is taken both as confirming the diagnosis and as the signal for venesection treatment to begin. Initially, one unit of blood (450ml) is taken every week. This may need to be done for up to two years. Once ferritin concentration is reduced to 20 micrograms per litre or less and transferrin saturation to 16% or less, the number of venesections can be reduced to between three and eight per year.

A genetic change in a gene called HFE has been identified. In the UK, 90% of haemochromatosis sufferers are homozygous for HFE. A genetic test for this mutation can be used to confirm diagnosis as well as to identify family members at risk from iron overload. In addition to brothers and sisters, children carry a significant risk of inheriting the disorder: since the heterozygous state is so frequent it is not uncommon for a person homozygous for haemochromatosis to have a partner who is heterozygous and thus for each of their children to be at 50% risk of having the condition.

Many see a strong case for population screening to detect the condition pre-symptomatically. As was recently argued by the Wessex Haemochromatosis Group: ‘Population screening for iron overload has been investigated and modelled, and a large prospective trial should be conducted. Population screening for hereditary haemochromatosis has attracted international interest; we hope that it will attract the attention of national

bodies.¹⁷ Before such screening could be undertaken, they go on to argue, 'studies are needed to establish the natural course of the genetic mutations... and the best screening test and optimal screening strategy.' A study based on blood samples given by 10 000 blood donors in South Wales led by Professor Mark Warwood and Dr Anthony Napier should hopefully begin to provide some of the information needed when the results are in.

As our case studies show, non-diagnosis remains the biggest problem facing patients. Once diagnosis has been made, a patient is likely to see a haematologist and a range of other specialists, dependent upon the extent of their symptoms. A patient support group, the Haemochromatosis Society, was formed in 1990. Its main aims are to raise professional awareness and to offer assistance to individual patients.

Haemochromatosis Case 1

A man in his early 40s, living in Greater London. Up until last year he worked as a manager with a major automotive company. Now he is unable to work due to a wide range of haemochromatosis-related symptoms.

"I started to get pains in my fingers 20 years ago. Writing is now a very painful process, and my whole hand will sometimes 'lock-up' completely, leaving me in excruciating pain. Other repetitive tasks are also very painful. Some ten years ago I started to get quite severe chest pains; on two occasions I was admitted to hospital only to be discharged after a few days. On the last occasion I was told that the pains were due to 'pre-marital nerves'! The pains gradually became more severe, but I did not return to hospital as I could see myself being labelled as a time waster. Approximately eight years ago I found myself having periods of sickness, particularly after drinking red wine or after an Indian meal. At about the same time I found myself needing considerably more sleep than usual; an afternoon nap / sleep became essential. At the time I just thought the ageing process was beginning to slow me up. I also began to suffer epistaxis (nose bleeds) and non-specific abdominal pains." Today all his joints, with the exception of the spine, are affected to such an extent that his mobility is affected – on bad days he needs to use a wheelchair. Writing just his name can be a very painful process. He is quite forgetful and often extremely tired and lethargic; about 50% of the time he will sleep for up to 20 hours per day. However, usually this does not really refresh him.

Being accused of having 'pre-marital nerves' was but one instance of non- / mis-diagnosis. One consultant asked him Just how many consultants did he want to see? The general message was that he was a malingerer; in reality he was more of a 'workaholic'. It was an Australian GP who first suggested haemochromatosis, but upon referral the consultant gastroenterologist just laughed and said: "no-one gets that, you only get it on doctors' examination questions." A confirmed diagnosis only came much later after he collapsed at home and was admitted to hospital. Three weeks of tests eventually led to a diagnosis of haemochromatosis after a liver biopsy. This came many years after the beginning of symptoms. *"When I was at my worst, around the time of diagnosis, I actually thought I might die. I felt so sick and had pain throughout my joints and abdomen. The doctors would look at me sympathetically while saying there was*

nothing they could do. Eventually, I was given strong anti-emetics and analgesia. This went some way to improving how I felt."

Even after the diagnosis was made, the consultant showed no interest in the condition, or him. He was given no information about haemochromatosis or about his medium- to long-term prospects. When he asked to have a liver scan performed he was told there was no need. He returned to his GP, whereupon a referral to a different hospital led to a scan straight away. His is now happy with his care, which is co-ordinated by his GP and a consultant liver specialist. He also sees a specialist in arthritis; a haematologist who bleeds him regularly; and a consultant oncologist who also specialises in pain and pain control. The Haemochromatosis Society has also helped him a great deal: *"within days of contacting them I had an endless supply of good information. I was also able to contact other sufferers. The knowledge and information gained gave me the light I needed to fight the illness."* Some family members have gone for testing, others have not. He doesn't think that the issue has been pushed enough by the professionals he sees. In his view, it is the older doctors who are the worst offenders – *"the younger doctors are interested and ask me for information on the condition and its treatment."*

Haemochromatosis Case 2

A man in his early 40s, living in the Midlands

"The problem first came to light three and a half years ago, when I was flushing excessively. My GP, on examination, found that my foreskin was too tight. He told me that I needed circumcision. Whilst having this operation the consultant took some blood for analysis and discovered that my testosterone level was excessively low. He therefore referred me to a consultant physician at another hospital. A series of tests – including brain scans, blood tests, bone density scans and various tests for diabetes – were performed over the next three months." After a while the consultant diagnosed a damaged pituitary gland as the cause of the reduced testosterone levels, and linked this to haemochromatosis via an understanding of the harm caused by raised iron levels to the pituitary gland. Family follow-up has revealed that a brother and sister have the condition, as well as his mother.

The diagnosis of haemochromatosis allowed some other problems to be explained: he had previously been treated for problems with his left shoulder and knee – at one point a major shoulder operation had been suggested – which on reflection could have been due to haemochromatosis. He had also been unusually emotional, which he had put down to the effects of a his marital break-up, but which he now feels could also have been due in part to his reduced levels of testosterone.

The most difficult aspect of the treatment *"was the weekly venesections I had to endure for over two years, particularly when, after the first three months, I had major problems with the veins in my arms resulting in several Hickman lines having to be inserted both in my groin and chest in order for blood to be withdrawn. This was quite a revolutionary treatment for someone in my condition, but as you can imagine it rather inhibited my physical activity."*

"The best aspect of the medical services I have received (bearing in mind that I have been very fortunate to be in the position to have

private treatment, which the rest of my family have not) is the care and attention my haematologist has given me.” Private health cover has enabled him to see the consultant haematologist most weeks. In addition to treating him, he has helped to co-ordinate the care provided by a number of other specialists: a cardiologist, a rheumatologist, an endocrinologist, an orthopaedic surgeon and a urologist. *“Being of the same age group as myself, we have become good friends and because I was the first to be diagnosed with haemochromatosis at the hospital it has raised awareness both at this facility and at the local regional hospital where I am treated for the pituitary problem.”*

Haemochromatosis Case 3

A woman in her early 40s, living in North-West England. She has a brother and a sister.

“In October 1982 my mother died at the age of 45. As children we had watched her go from a lively mum to an extremely tired mum who could have slept the clock around. She even had trouble walking as a result of pain throughout her body, although she always had a lovely tan. When she died we questioned the cause of death, haemochromatosis, only to be told by our GP that she had died from an extremely rare condition and that to be on the safe side our family should be screened. He also said that the chances of us having it were virtually nil.”

But testing revealed that she and her brother had both inherited the condition. A liver biopsy showed it to be unaffected, but her iron load was already elevated. At the time she had no symptoms except a little tiredness. Since then, despite regular venesections, many of the symptoms of haemochromatosis have developed. She suffers from tiredness and a ‘foggy’ head; muscle pain; arthritis in both knees and the left ankle; and soreness in her elbows, wrists and knuckles. These latter symptoms are a particular problem as she works as a typist.

Initially she met a lot of scepticism and ignorance about the condition. But, *“luckily I was in the position to access medical books, journals and papers from the medical library at the hospital where I work. Also I was not afraid to ask questions, although the majority of people would ask me ‘haemo what?’ I found that I had to educate some medical people as well as everyone else. A locum GP even told me that the cure for haemochromatosis was promptly to whip out the pancreas. Needless to say I soon put him right.”*

Her sister was diagnosed as not suffering from haemochromatosis. In fact doctors said that she was anaemic, and put her on iron tablets. *“Last year I became very concerned about her. She had become increasingly fatigued only to be told again that she was anaemic and that her intake of iron tablets needed to be increased to three per day. I insisted that she have the genetic test for haemochromatosis. This proved that she did in fact have the condition. What had been happening was that because of gynaecological problems she had been losing more blood during periods than the average woman, so that when her iron levels were tested they were low. If she hadn’t had the genetic test, any problems that developed later in life might have been missed. At this point I should point out that our mother had been given iron tablets and iron injections for the last 22 years of her life.”*

“My experiences have only increased my determination to ensure that

GPs and also the general public are better informed about the seriousness of the condition if it is allowed to go undiagnosed. I have recently set up a local patient’s group for the Merseyside area to spread the word.”

Haemochromatosis Case 4

A man in his early 50s, living in Southern England.

When he was 45 a BUPA ‘Well Man’ check-up revealed that he had a high serum ferritin concentration. A referral to a local consultant led to a diagnosis of the disorder following a liver biopsy. At this point he had none of the symptoms associated with haemochromatosis. Initially frequent venesections were introduced to control his ferritin levels. These are now performed four-monthly and are accompanied by a general medical check-up. He is still largely symptom free: he occasionally feels a little tiredness and has some soreness in his knees, but nothing too severe, and both may be unrelated to his tendency to iron overload.

He has two sons in their mid-twenties. Both have tested negative on blood tests. However, genetic tests have recently revealed that his wife is a carrier for haemochromatosis, which means both sons are at 50% risk for the homozygous state. They are currently considering if and when they might go for genetic tests – medically they see the need, but concerns about the insurance implications are making them a little cautious.

Haemochromatosis Case 5

A man in his late 40s, living in Northern Ireland. He worked as a professional actor for many years but had to give it up in 1990 because of the effects of haemochromatosis.

“It was in the mid-1980s that I began to have lots of problems with my health. I became prone to infections. I suffered from various aches and pains, specifically joint pains: my ankles and knees would give way. I also suffered from fevers and sweats, memory loss and general exhaustion. Today, after about 50 venesections, I still suffer from joint pains, especially in my legs, memory loss and general fatigue. I also get chest pains now.”

“For a number of years I was mis-diagnosed locally, both by my GP and the hospital. But while in Canada in the early- to mid-1990s I was quickly diagnosed by a rheumatologist. My local doctors were really unpleasant when I told them that Canadian doctors had found the cause of the illness. Initially I was quite uneasy to be under their care again. But now I must admit that I feel that knowledge of the disorder is at last seeping in and I am now in the care of a consultant in Internal Medicine and also a cardiologist who are on top of the situation.”

On the whole however, despite the recent improvement, he is very critical of the service he received: *“I found that not only were many specialists and general doctors ignorant of what to look for, but also arrogant and disbelieving when I told them. This was hard to take when I ended up with a poorer quality of life because of them.”* Despite the fact that he has been diagnosed and that two of his brothers died within two weeks of each other in 1990 from what now appears to him to be iron overload-related problems – liver and heart disease – his remaining brothers and sisters have tended not to pursue the issue. But in his view many

more people should be encouraged to take the tests for the condition: *“Finding this common disorder in people requires a very simple test and I think this should be done on everyone. Not only the individual but also the health service would benefit – just imagine the savings that would be made over the lifetime of an individual.”*

3 Discussion

3.1 The Importance of Diagnosis

Diagnosis – having a name for what has happened to you or to your children, is for many families an essential part of understanding and coming to terms with the situation in which they find themselves. The absence of a diagnosis can leave people vulnerable to feelings of guilt or recrimination. It may also lead families down inappropriate routes in their search for an explanation and support which can be a source of great confusion and frustration. The lack of a diagnosis may lead to an unnecessary deterioration of the patient's condition. Its prompt availability is the first step towards appropriate care and treatment.

Familial hypercholesterolaemia illustrates well some of the consequences of non-existent or inadequate diagnosis. In the fifth case example, diagnosis could and should have been made much earlier. As the patient put it: *"Five years ago this should have been picked up. I'm not saying I wouldn't be in this position now, but I could have taken preventative measures earlier."* Of course, some people with familial hypercholesterolaemia do not suffer the frustrations of knowing something is wrong for the simple reason that a severe cardiac event comes out of the blue. However, intense frustration, as well as deterioration in their condition, is the norm for undiagnosed haemochromatosis patients. Consider for example the first and the fifth haemochromatosis cases. In both cases many years of steadily worsening symptoms failed to prompt a diagnosis; and when one was eventually made, the initial reaction from some professionals was still scepticism.

Lack of, or incorrect, diagnosis is a problem for tuberous sclerosis and neurofibromatosis patients also, although thankfully the 15 year wait in the fifth neurofibromatosis case is an extreme example. But what the cases also illustrate is an under-appreciation of the implications of the conditions, on the part of both non-medical authorities and some medical professionals. As the mother of the fifteen year old in the fifth neurofibromatosis case put it:

"I know NF1 is not widely known about, but the hardest thing was convincing the teachers at school; one pretty much laughed in our faces as he thought we were making excuses."

Blaming the family environment rather than understanding the behavioural implications of the disease process came up in two of the tuberous sclerosis cases. In the first case, when the whole family visited a family psychologist, they were asked: *"How can you expect your children to respect you if you don't respect yourself?"* This attitude set the pattern. Professionals tended to reject the mother's references to TS as excuse making. In the third case, social services put the young boy's complaints and symptoms down to a behavioural disorder. They were, and still are, more interested in his 'identity' problems than his headaches. These responses have continued despite the fact that, after a fit in 1994, he was diagnosed as having TS after a CT scan at the local hospital.

Tuberous sclerosis is a particularly difficult genetic condition to manage, and the cases given in this report are ones that have been handled badly. They are not however atypical ones. They highlight that it is not just educational and social services, but

also some medical professionals, who have difficulties taking a holistic view of the condition. This has led the Tuberous Sclerosis Association to place an emphasis on referral to TS clinics for accurate diagnosis and case assessment, an issue we will return to later.

It is a common feature of many of the stories told in this report that professionals are often sceptical about patient or parental anxieties and that they often make inappropriate recommendations based upon their assumptions about the nature of the problems as they see it. Without diminishing the difficulties 'generic' professionals experience in their everyday practice, a greater sensitivity to the fact that they will often come into contact with symptoms that may reflect the presence of an underlying rare disorder, and a greater willingness to consider this in working with patients and other professionals when planning their response would improve prospects of accurate diagnoses being made. Better health care would result.

In all of the conditions considered in this report, there are significant primary or secondary symptoms that, if detected early, can be treated or managed. The management of patients who are already symptomatic is discussed in section 3.3 below. But in familial hypercholesterolaemia and haemochromatosis, a liability to develop symptoms can be tested for before the damage is done. The case for more pro-active screening is made in sections 2.3 and 2.4. The contrast between the Haemochromatosis cases detected early and those that went undiagnosed for many years speaks for itself. There is of course the danger of adding to the problem of the 'worried well' patient. But the selective offering of pre-symptomatic tests for these conditions seems justified by the best evidence we have, which indicates that the penetrance of the genetic mutation is significant in both cases, as is the efficacy of early treatment. At the very least, the Department of Health should formulate a protocol to encourage family follow-up in these conditions and to encourage more research at the population level.

Recommendations

When the penetrance of a genetic mutation is significant and early treatment is efficacious, the selective offering of pre-symptomatic tests seems justified. The Department of Health should formulate protocols to encourage family follow-up in these conditions and to encourage more research at the population level (3.1).

3.2 The Problem of Inadequate Referral

Accessing the right level of expertise is the route to establishing an accurate diagnosis and programme of disease management and treatment. Problems due to non- or inadequate diagnosis often result from an inadequate referral. Once this has happened, it can prove difficult to secure an appropriate referral at a later date. As a result, both the initial diagnosis and the ongoing care may be sub-standard. Conversely, as the third neurofibromatosis case illustrates, an appropriate referral lays the basis for care, which both satisfies the family and uses different levels of specialism within the NHS effectively.

In the case of familial hypercholesterolaemia, inadequate referral can often result from a GP failing to see a genetic link

and the specific benefits that result from treatment based on this monitored by a lipid clinic. The fifth case study is sadly not unusual. Despite visible signs of FH, and the fact that his father had died of a heart attack, an appropriate referral, and hence treatment, was not arranged. An analogous situation often occurs in which a woman is told by the GP not to worry about her children's health despite the fact that her husband and his father both died young of heart disease.

In patients with FH, the total cholesterol level can be a poor guide to the underlying risks. What may appear to be a marginal risk may in fact be much greater. The GP's advice to the patient in the second case, to not worry too much but to watch what he ate, was based on an unexceptional total cholesterol level reading of 6.8. But what he hadn't picked up on was the elevated LDL level, which, given a family history of heart disease, was indicative of familial hypercholesterolaemia. This is a specific example of a more general problem: treatment and referral guidelines drawn up for the population as a whole sometimes fail to take into account specific genetic factors which call for a different protocol. Guidelines by their very nature cannot cover all eventualities, but where the generally appropriate course of action leads to outcomes which are adverse for a specific subset of the population this should be indicated if patients are not to be disadvantaged.

In all five cases of tuberous sclerosis discussed in this report the family have had problems securing a complete and thorough range of referrals. In the first case, it wasn't until the son was ten that he saw a paediatric neurologist, who has now arranged a referral to a specialist at a London hospital to assess the growths and lesions on the brain. In the fourth case, treatment was effectively refused until it was almost too late. In all the other cases the family has had to struggle to secure a referral to a specialist clinic – not always with success. The difficulties which the families have reported in these five instances would be very familiar to many members of support groups for those with rare genetic disorders and are symptomatic of a common problem.

Problems with referrals are often due to a combination of a continuing reluctance to refer out of area and a GP or a physician at a local hospital not appreciating that input from a genetic- or disease-specialist could add to the assessment of the patient. What measures can be taken to improve initial diagnosis? After all, for any kind of referral to take place, a diagnosis must be made, or at least suspected. And what can be done to guide non-specialists on the most appropriate referral?

At any one time, the average GP is likely to have no more than one person on their books with neurofibromatosis. Similarly, as one of our case studies shows, a district hospital may have little experience dealing with haemochromatosis. Given that NF1 and haemochromatosis are two of the more common of the single gene disorders, it is easy to see why prompt diagnosis can be a problem. One idea being pioneered in The Netherlands by VSOP, a patient group, is a decision-tree CD-ROM based on symptoms exhibited. Targeted at GPs, the aim is not to replace specialist services, but rather to improve referrals to them. The same system could document the existence and geographical spread of specialist clinics and other regional experts and how demand can be managed to make best use of scarce expertise in

order to maximise the opportunities for families to receive appropriate expert help. Such a system would have to address the role of specialist clinics and regional experts if it was not to be swamped with inappropriate referrals, or result in patients and their families having to travel long distances to have issues resolved that could more appropriately and effectively be managed locally. This could be achieved by a series of small scale consensus conferences, analogous to those carried out by the National Institutes of Health in the USA, but focusing on the specific determinants of good clinical practice relating to the management of a particular condition or disorder by the NHS.

Recommendations

One idea being pioneered in The Netherlands by VSOP, a patient group, is a decision-tree CD-ROM based on symptoms exhibited. Targeted at GPs, the aim is not to replace specialist services, but rather to improve referrals to them. The same system could document the existence and geographical spread of specialist clinics and other regional experts. The Department of Health should commission the production of a similar product for the UK (3.2).

Guidelines or protocols developed for the management of common disorders should also make reference to specific aspects of rare genetic conditions to which the generally approved course of action does not apply and who may need different or more extensive investigation to determine the most appropriate treatment. For those patients in this latter category small scale consensus conferences should be used to establish good clinical practice and determine those elements of the condition that are best managed locally and those which need more specialist help. (3.2)

3.3 The Role of Specialist Centres

Single gene disorders, of which there are around 5000, are a significant source of ill health. Individually, however, they are relatively rare. To capture the range of expertise necessary to deal with this combination of collective burden and individual rarity, clinical genetic centres operate on a regional basis as specialist centres drawing from a large population base, as outlined in section one of this report. Other specialist clinics, perhaps with input from clinical geneticists, have developed to manage specific disorders. These are 'virtual' clinics in the sense that they do not have permanent staff and buildings, but are rather a group of specialists who meet at regular intervals.

As outlined in section 2.1, tuberous sclerosis clinics exist across the UK. In addition to clinical geneticists, neurologists, psychiatrists and renal medicine specialists form the core of the typical clinic. In the case of neurofibromatosis there are three clinics in existence or in the process of formation: in Cambridge, Leicester and Sheffield. All three include a geneticist. Other specialists involved include paediatric neurologists, paediatric endocrinologists and paediatric ophthalmologists. There are also plans or ideas for further clinics, and individual specialists in NF provide a service akin to a specialist clinic.

The appropriate specialist centre for patients with familial

hypercholesterolaemia is a lipid clinic, of which there are 156 in the UK. There are no specialist clinical centres for the management and treatment of haemochromatosis. However, and this holds for the other conditions as has already been indicated, there are many individual specialists with knowledge of the condition working across the UK. Without diminishing the value of these individual specialists and the contribution they make to supporting families, the breadth of their knowledge and their ability to sustain the comprehensive provision across a range of interventions needs to be considered, given the complexity of many multi system genetic disorders.

A multi-disciplinary clinic can play a number of roles. It can act as a 'one-stop shop' to establish a diagnosis and base-line assessment (prognosis); It can act as an ongoing source of expertise to a GP or physician; and it can play an ongoing, more hands on, role in disease management. From the patient point of view, it is the quality of the diagnosis and the management of their care and treatment that matter. Where clinics exist, a referral to them might raise the quality of the care. It also means that during the process of diagnosis and perhaps monitoring they don't have to see many different specialists at different times; thus increasing the likelihood of consistent advice and support being given and reducing the need for patients to use their own energies and resources communicating with different people at different times and in different places.

The clinic model offers many advantages from the patient's point of view, but whether or not a clinic-based approach is adopted more widely, the quality of care offered by a system involving a multi-disciplinary clinic should act as a benchmark for all clinical practice. At the very least, in each region, or nationally for the very rare conditions, there should be a designated professional expert in the condition. They should be accessible for advice on disease management even if they are not able to take direct referrals.

Although multi disciplinary clinics offer many advantages they can impose a significant burden on patients and families attending them. Time away from work, possibly coupled with loss of earning, and the expense of rail fares and sometimes overnight accommodation can put a financial strain on families already struggling to meet the additional costs of disability or chronic ill health. Although many are willing to travel long distances to get expert help and will put themselves to considerable expense and inconvenience to do so, there are those who cannot do this, and they should not be disadvantaged in their access to help and support. Nor should the willingness of families to use their own resources to secure the best for their affected family member be exploited carelessly – for example by arranging appointments that preclude the use of cost reducing options such as cheaper rail tickets.

New technology, particularly the use of Internet based communications and telematics should facilitate the building up and maintaining of registers of expertise and also ensure ease of access to it without constraint. Of particular benefit might be the development of truly virtual clinics, which do not require the physical presence of a range of experts with scarce skills. With co-ordination, a national expert could make a simultaneous input into a number of consultations in different

locations by means of the electronic transmission of data and images. For this to be effective there would need to be agreement as to what aspects of a condition could best be managed at local level and what would benefit from more specialist advice.

In the case of tuberous sclerosis, the experiences of families indicate that a patient should be seen at least once by a TS clinic. This establishes a base-line assessment and creates a line of communication between the clinic and the principal clinician managing the patient's care. The principal clinician may be a member of the TS clinic. Although this is desirable, in practice this is unusual. After this, an annual check-up, perhaps at the clinic, should be formalised to monitor the principal symptoms and determine whether any new ones have developed, with the emphasis on monitoring those that are significant, relatively common and more easily managed when found early.¹⁸

This model is also relevant for many other conditions. In their authoritative study, David Gutmann and Francis Collins advocate the formation of neurofibromatosis clinics closely allied to relevant disease specialisms.¹⁹ One role for such clinics would be to establish a benchmark assessment of the patient and their needs. As Susan Huson tells us, because organ involvement and its severity vary between NF1 patients, 'definition of the correct level of care for NF1 patients is difficult.'²⁰ Whether clinics have a role to play beyond this initial benchmarking exercise is a point of debate. Some argue that specialist clinics should monitor the patient for the emergence of complications. Others take the view that this is unnecessary, perhaps unhelpful, in that it will raise anxiety while offering little or no clinical benefit. As Huson summarises it: 'Another view, based on experience in a South Wales population study that revealed that most complications occurred very infrequently and would not be treated pre-symptomatically, was that patients should have annual outpatient checks but nothing more specific unless there were symptoms.'²¹ In general, more monitoring is required in childhood than in adulthood as complications are likely to emerge earlier rather than later. The Neurofibromatosis Association recommends an annual clinical review and supports the formation of clinics, but recognises that not all patients will need regular referrals.

Recommendations

Multi disciplinary clinics offer many advantages from the patient's point of view. Whether or not a clinic-based approach is adopted more widely, the quality of care offered by a system involving a multi-disciplinary clinic should act as a benchmark for all clinical practice. At the very least, in each region, or nationally for the very rare conditions, there should be a designated professional expert in the condition. They should be accessible for advice on disease management even if they are not able to take direct referrals. IT based systems for the provision of 'virtual' clinics should be developed and made the subject of a pilot experiment. (3.3)

3.4 Co-ordinating Treatment and Care

In the previous section the emphasis was on a multi-disciplinary approach to aid diagnosis, prognosis and the care and treatment of the patient. An important aspect of this is the ongoing

co-ordination of patient care. As the examples show, when this is done well – which in practice seems often to be due to an individual clinician taking a personal interest – it significantly improves people’s lives. Conversely, when no one takes responsibility for co-ordinating care and communicating with the patient and the family, the standard of care as well as the whole family’s sense of well-being is likely to deteriorate. The contrast is evident in the highs and lows of the family in the first neurofibromatosis case study.

During childhood a paediatrician might play the role of a generalist with an overview of the patient’s condition and care, whereas in adulthood there is rarely an equivalent. Sometimes no one will play a co-ordinating role. In other cases a specialist with a limited perspective on the condition might have responsibility. One of the complaints of tuberous sclerosis patients, for example, is that organic disease processes are sometimes neglected in favour of psychological explanations of the behavioural symptoms. This might be accentuated when the principal clinician is a psychiatrist. In general, genetics departments are not set up, or are not adequately funded, to play a broader clinical role in relation to co-ordinating the management of patient care. One solution would be to resource genetic services to enable them to play this role for more conditions than is currently the case; but for the reasons outlined in the introduction, (1.3) this might be difficult to achieve in practice without the development of policies and practices, and the allocation of adequate resources to ensure that this could happen effectively.

In practice, a disease specific or organ specific consultant, or perhaps a geneticist, the patient’s GP and the patient and his or her family often end up sharing responsibility. In order to build on this pattern, the notion of care pathways has been put forward as a model. Certainly, if practice were brought up to the standards proposed in some of the models, that would be a big improvement. But care pathways are sometimes like spokes without a hub: what is needed is a focus; and whoever it is that provides the focus by taking the lead in co-ordinating the patient’s care must be recognised by others involved as doing so and the direction and impetus they provide to integrate service provisions accepted and acted on by all the stakeholders in the process.

3.4.1 An adult ‘paediatrician’?

When a patient and the family strike up a good relationship with an individual clinician they acquire a focus for their healthcare. If we return to the first neurofibromatosis case we can see how important this is.

The care is now divided between four teams: the surgeon near London who checks her leg once a year; a paediatrician who does an annual check up and generally looks after her; a team from the hospital that fitted the shunt, who perform six monthly check ups on her head; and a local ophthalmologist for her astigmatism. The mother is full of praise for the paediatrician: *“He treats her as a whole person”*. When there are problems to sort out or reports to write for school she goes to him: *“He’s like my right hand man”*.

It is hard to legislate for right hand men, but we all like them when we find them. The paediatrician is looking out for the best interests of the child in the clinical and the everyday sense of the term. What adults need is their own version of a good paediatrician. At the very least, what they need is a principal clinician who can take an overview. In some circumstances, a geneticist, or the regional genetic service as a whole, will play this role. In Manchester for example, the regional genetic service has offered annual monitoring to adults with neurofibromatosis. In others, the physician who deals with a major symptom could be given the responsibility.

In some areas, for some conditions, it might be possible to mimic the childhood situation more explicitly, through the development of adult generalists. In an age of specialists, this might appear to be a step back into history. But one of the interesting, if very anecdotal, findings of the patient interviews is that such generalists, play a valuable role in recognising patterns in multi-organ disorders. The role of specialists in internal medicine, which has emerged in Canada, provides a possible model, which might be developed, for use in the NHS. As well as multi-system disorders, this model could also have benefit in the management of clusters of related conditions, such as metabolic disorders for example. An existing unit in London and others in the process of formation elsewhere would indicate that the need for such a role is already recognised in the UK. A study of how other countries use such specialists would be a useful addition to the UK policy debate in this area.

Whoever it is that plays the role for each condition, service specifications for the principal clinician should be drawn up and the commitment of all other stakeholders to ensuring the effective implementation of agreed outcomes for the patient and their family secured.

Recommendations

Care pathways are sometimes like spokes without a hub: what is needed is a focus; and whoever it is that provides the focus by taking the lead in co-ordinating the patient’s care must be recognised by others involved as doing so. In the same way that a paediatrician is able to take a holistic overview of the management of the medical needs of children, adults too need a principal clinician who can also take an overview. Whoever it is that plays the role, for each condition, service specifications should be drawn up which acknowledge the range of disciplines necessary to achieve properly integrated care and the roles played by all the players in this orchestra. (3.4.1)

In some areas, for some conditions, it might be possible to mimic the childhood situation more explicitly, through the development of adult generalists. A study of how other countries use such specialists would be a useful addition to the UK policy debate in this area (3.4.1).

3.4.2 Care pathways: a role for the patient

Another solution, which should be seen as complementing rather than running counter to the importance of having a

primary medical contact, is for the patients themselves to provide a focus for the integration of care. It is often the case that the patient and the family are more informed about the condition and its associated problems than many professionals they meet. Giving them a formal co-ordinating role – and giving them shadow medical records – could help to focus their care. For this to work there would need to be more than just lip service given to the notion of patient empowerment. The NHS would need to recognise the potential benefits that would result, not only for the family but also for the professionals and the health service. Benefits resulting from patients feeling more in control of their lives would not be confined to the NHS. Clearly the health gain from properly integrated care, with different elements working together in a complementary position would potentially be significant. The broader economic and social benefits for families that comes from the knowledge that they are benefiting from current best practice and so able to get on with managing their lives, given the limitations imposed by 'their' condition, are also important - as are the spin-offs for the work of Education and Social Science departments too. A trial to test this out would be a useful experiment. In this scenario, family care workers would take on an enhanced role.

Family care workers have been appointed by a number of patient groups to work alongside professionals in the NHS. Where these exist they support the patient and family in a variety of ways – from taking the time to explain the condition, perhaps calming a newly-diagnosed family down after they have read about worst case scenarios on the Internet, to fighting their corner with social services or the local NHS to achieve an adequate referral. As they acquire the necessary medical knowledge their role can evolve into a cross between a patient advocate and a practice nurse. In large part, patient support groups pay for these workers. To maintain their role as advocate many wouldn't want the NHS to pay them in full, but a sharing of the cost is appropriate given the mixture of roles they play.

Recommendations

Another solution, which should be seen as complementing rather than running counter to the importance of having a primary medical contact, is for the patients themselves to provide a focus for the integration of care. Giving them a formal co-ordinating role and the authority to exercise this – and giving them shadow medical records – should be tried as a pilot programme. A necessary first step in this would be to establish a culture-change such that professionals are more willing to listen to and respect the ideas of patients and reduce the tendency to regard those who want to be actively involved in the management of their situation as unhelpful. This, in itself would reduce the frustration reported by a number of individuals and families in this report. (3.4.2).

In order to maintain their role as advocate some voluntary groups would not want the NHS to pay family support workers in full, but a sharing of the cost is appropriate given the mixture of roles they play. Arrangements for funding condition specific family support workers (traditionally the sole responsibility of patient support groups) which recognise the importance of their independence from mainstream NHS

management systems and which allows them effectively to act as advocates arguing for the provision of integrated care and support for families with rare genetic disorders should be made. Cost sharing would be an appropriate way forward possibly using the additional resources available for health from the National Lottery when the Millennium Fund is wound up. (3.4.2)

Recommendations

- Given the rarity of many single gene disorders it is difficult for health service planners to gather evidence with the necessary degree of scientific rigour to meet the criteria advocated by Cochrane for the evaluation of effective practice. This makes the experience of families presented in this report all the more important for validating practice. The NHS should ensure that it is able to recognise the value of user experience as a deterrent of quality and effectiveness. (1.3)
- The experience of many families is of delayed or absent diagnosis, non-referral to sources of expert help and inadequate social support. Too often agencies and different clinical specialisms fail to communicate effectively (or even at all). Protocols, guidelines and other mechanisms to enable generic practitioners to gain access to expert advice promptly and effectively are needed (2.1).
- When the penetrance of a genetic mutation is significant and early treatment is efficacious, the selective offering of pre-symptomatic tests seems justified. The Department of Health should formulate protocols to encourage family follow-up in these conditions and to encourage more research at the population level (3.1).
- One idea being pioneered in The Netherlands by VSOP, a patient group, is a decision-tree CD-ROM based on symptoms exhibited. Targeted at GPs, the aim is not to replace specialist services, but rather to improve referrals to them. The same system could document the existence and geographical spread of specialist clinics and other regional experts. The Department of Health should commission the production of a similar product for the UK (3.2).
- Guidelines or protocols developed for the management of common disorders should also make reference to specific aspects of rare genetic conditions to which the generally approved course of action does not apply and who may need different or more extensive investigation to determine the most appropriate treatment. For those patients in this latter category small scale consensus conferences should be used to establish good clinical practice and determine those elements of the condition that are best managed locally and those which need more specialist help. (3.2)
- Multi disciplinary clinics offer many advantages from the patient's point of view. Whether or not a clinic-based approach is adopted more widely, the quality of care offered by a system involving a multi-disciplinary clinic should act as a benchmark for all clinical practice. At the very least, in each region, or nationally for the very rare conditions, there should be a designated professional expert in the condition. They should be accessible for advice on disease management even if they are not able to take direct referrals. IT based systems for the provision of 'virtual' clinics should be developed and made the subject of a pilot experiment. (3.3)
- Care pathways are sometimes like spokes without a hub: what is needed is a focus; and whoever it is that provides the focus by taking the lead in co-ordinating the patient's care must be recognised by others involved as doing so. In the same way that a paediatrician is able to take a holistic overview of the management of the medical needs of children, adults too need a principal clinician who can also take an overview. Whoever it is that plays the role, for each condition, service specifications should be drawn up which acknowledge the range of disciplines necessary to achieve properly integrated care and the roles played by all the players in this orchestra. (3.4.1)
- In some areas, for some conditions, it might be possible to mimic the childhood situation more explicitly, through the development of adult generalists. A study of how other countries use such specialists would be a useful addition to the UK policy debate in this area (3.4.1).
- Another solution, which should be seen as complementing rather than running counter to the importance of having a primary medical contact, is for the patients themselves to provide a focus for the integration of care. Giving them a formal co-ordinating role and the authority to exercise this – and giving them shadow medical records – should be tried as a pilot programme. A necessary first step in this would be to establish a culture-change such that professionals are more willing to listen to and respect the ideas of patients and reduce the tendency to regard those who want to be actively involved in the management of their situation as unhelpful. This, in itself, would reduce the frustration reported by a number of individuals and families in this report. (3.4.2).
- In order to maintain their role as advocate some voluntary groups would not want the NHS to pay family support workers in full, but a sharing of the cost is appropriate given the mixture of roles they play. Arrangements for funding condition specific family support workers (traditionally the sole responsibility of patient support groups) which recognise the importance of their independence from mainstream NHS management systems and which allows them effectively to act as advocates arguing for the provision of integrated care and support for families with rare genetic disorders should be made. Cost sharing would be an appropriate way forward possibly using the additional resources available for health from the National Lottery when the Millennium Fund is wound up. (3.4.2)

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