Improving awareness of monogenic diabetes through a specialist genetic diabetes nurse

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Article points

1. Monogenic diabetes is poorly recognised but identification is important in order to ensure that people are receiving the correct treatment.
2. In order to improve recognition of monogenic diabetes the national Genetic Diabetes Nurse (GDN) project was set up in 2002 (Shepherd et al, 2005). GDNs aim to increase knowledge of monogenic diabetes through presentations and identify possible cases to refer for genetic testing.
3. Appointing a GDN in the Sussex area improved care through the identification of 54 people with monogenic diabetes and the establishment of a specialist monogenic diabetes clinic.

Key words

- Genetics
- Monogenic diabetes
- Genetic testing

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Monogenic diabetes is poorly recognised but identification is important as many people may be successfully managed with sulphonylureas rather than insulin (Pearson et al, 2000; Stride and Hattersley, 2002; Pearson et al, 2003; Shepherd et al, 2003; Hattersley, 2005). Ensuring the correct diagnosis also allows appropriate follow up and counselling of family members (Shepherd et al, 2010). The Genetic Diabetes Nurse (GDN) project was set up in 2002 to increase awareness of monogenic diabetes (Dudding et al, 2005; Shepherd et al, 2005) and prior to the appointment of a GDN for Sussex in 2005, only one person had a confirmed diagnosis of monogenic diabetes in the Brighton and Hove area. This paper describes how training a GDN improved care through the identification of 54 people with monogenic diabetes and the establishment of a specialist clinic.

The Royal Sussex County Hospital within Brighton and Sussex University Hospitals Trust has an acute diabetes service which manages over 2000 people with type 1 diabetes and other people with more complex diabetes care requirements. There are also well-developed primary care services supported by a community diabetes team. In 2005, there was only one person previously referred from Brighton with confirmed monogenic diabetes (caused by a mutation in the *HNF1A* gene). Molecular genetic testing for monogenic diabetes has been available at the Royal Devon and Exeter NHS Foundation Trust since 2000, although referral and detection varies widely across the UK (Shields et al, 2010).

Improving recognition

In order to improve recognition of monogenic diabetes, the national Genetic Diabetes Nurse (GDN) project was set up in 2002, led by Dr Maggie Shepherd and the Exeter monogenic diabetes team (Shepherd et al, 2005). The GDNs are a team of experienced DSNs who receive specific ongoing training in the identification, management and treatment of monogenic diabetes (Dudding et al, 2005). Identifying people with monogenic diabetes can be straightforward if healthcare professionals are familiar with the key characteristics (*Table 1*).

GDNs aim to increase knowledge of monogenic diabetes through presentations to other healthcare professionals and identifying possible cases to refer to Exeter for genetic testing. Detecting these potential cases is important as this can result in transfer from unnecessary insulin injections to sulphonylureas (Pearson et al, 2000; Stride and Hattersley, 2002; Pearson et al, 2003; Hattersley, 2005; Thanabalasingham and Owen, 2011) and appropriate follow up of other family members (Shepherd and Hattersley, 2004; Shepherd et al, 2009).

This paper describes the impact of a GDN within the Brighton and Hove area in the identification of people with monogenic diabetes and the establishment of a specialist monogenic diabetes clinic.

Aims

To evaluate the effectiveness of appointing a GDN in identifying people with monogenic diabetes and developing a specialised service to meet their needs.

Method

An experienced DSN was seconded to the national GDN team from the Royal Sussex Country Hospital, Brighton for 3.5 hours per week in 2005. She attended introductory and ongoing training in monogenic diabetes in Exeter three times a year.

The GDN then delivered presentations to increase awareness of monogenic diabetes among diabetes teams in Brighton and Hove and across the surrounding areas. Audiences included primary, community, paediatric and secondary care diabetes teams, in addition to more generic forums, for example the regional DSN interest groups. Attendees were asked to complete evaluation forms following the presentations, which were returned to the Exeter team for collation and quality assessment. Attendees were also encouraged to consider people within their own practice who may fit criteria for monogenic diabetes; this included identifying people who may have maturity-onset diabetes of the young (MODY), which is typically diagnosed in people under 25 years with a parent with diabetes and evidence of ongoing endogenous insulin production, or neonatal diabetes (typically diagnosed below 6 months of age). Attendees were encouraged to refer these potential cases to the GDN for further discussion and investigation.

The electronic patient record widely used by both secondary and community care teams within the area was interrogated by the GDN with the intention of identifying possible cases.

Results

Presentations

Since the GDN started 7 years ago, 44 presentations have been delivered to over 950 healthcare professionals. Feedback indicated that 95.4% of attendees rated the presentations as "very good" or "excellent" for both educational value and quality. As a consequence of an increase in the awareness among colleagues of monogenic diabetes, referrals of people potentially considered to have monogenic diabetes to the GDN increased. These referrals included some long-standing unusual cases of diabetes and those tentatively considered likely to have monogenic diabetes. The GDN reviewed these cases and, where appropriate, discussed them with the Exeter team. Recommendations were made to conduct either pancreatic antibody testing or urinary c-peptide creatinine ratio (UCPCR) prior to consideration of genetic testing to aid differential diagnosis in many cases. For example, in people previously considered to have type 1 diabetes, within five years of diagnosis and likely to have some remaining endogenous insulin production, testing included glutamic acid decarboxylase (GAD) and insulinoma-associated-2 (IA2) pancreatic antibodies. If these tests were positive this confirmed autoimmune (type 1) diabetes. In contrast, in people previously assumed to have type 1 diabetes and more than five years post diagnosis, a UCPCR was advised in addition

Table 1. Key characteristics of monogenic diabetes.

Maturity-onset diabetes of the young	Neonatal diabetes
Diabetes diagnosed before 25 years of age in at least one family member.	Diagnosis of diabetes typically before 6 months of age.
A parent with diabetes.	No family history of diabetes is common as the majority of mutations are spontaneous.
Evidence of continued insulin production (for example, non-insulin dependent or c-peptide positive after 5 years post diagnosis.	Most commonly caused by mutations in the *KCNJ11*, *ABCC8* or *INS* genes.

Page points

1. In order to improve awareness of monogenic diabetes, a Genetic Diabetes Nurse was appointed in Sussex. The impact of this post was then assessed.
2. An experienced DSN underwent introductory and ongoing training in monogenic diabetes and was then asked to deliver presentations to other healthcare professionals in the area to raise awareness.
3. Feedback from healthcare professionals who attended the presentations was very positive and led to an increase in the number of referrals of potential cases to the GDN.

"A total of 48 people, who met the key criteria for MODY, were referred for genetic testing."

to testing for pancreatic antibodies. UCPCR levels greater than 0.2 nmol/mmol (indicating endogenous insulin production) in those with a diabetes duration greater than five years was suggestive of a non-type 1 diagnosis. People with negative antibodies and a positive UCPCR meeting the key criteria for MODY (*Table 1*), were referred for genetic testing.

A total of 48 people, who met the key criteria for MODY, were referred for genetic testing. Criteria were identified by ascertaining details of family history, age of diagnosis and additional clinical details. These people were advised that the Exeter team were looking for a specific genetic cause of their diabetes that could potentially have implications for their treatment and other family members.

When MODY was identified in these cases, diagnostic genetic tests were then offered to their family members within the Brighton and Hove area (28 individuals). Predictive genetic testing was requested by four individuals not known to have diabetes at the time (two *HNF1A*, one *HNF1B*, and one mitochondrial diabetes and deafness [MIDD]) and genetic counselling was provided in these cases. Follow up of other family members living outside of Sussex was organised through liaison with the Exeter team and other GDNs located elsewhere.

Electronic patient records

Unfortunately, the record of family histories was not routinely documented on the electronic patient record used in Brighton and it was therefore only possible to systematically screen for age of diagnosis and management with oral agents. Ten people diagnosed before the age of 30 years who were not on insulin treatment were identified through this search. One of these 10 people was subsequently confirmed to have *HNF1A* MODY but the remainder had BMIs between 38–44 kg/m^2 and other features associated with type 2 diabetes, so were not considered appropriate for genetic testing.

Identification of monogenic diabetes

A total of 54 individuals, referred from Brighton and Hove since 2005, have been confirmed by molecular genetic testing at the Royal Devon and Exeter NHS Foundation Trust to have a mutation in one of the genes known to cause monogenic diabetes. This includes 22 probands (out of

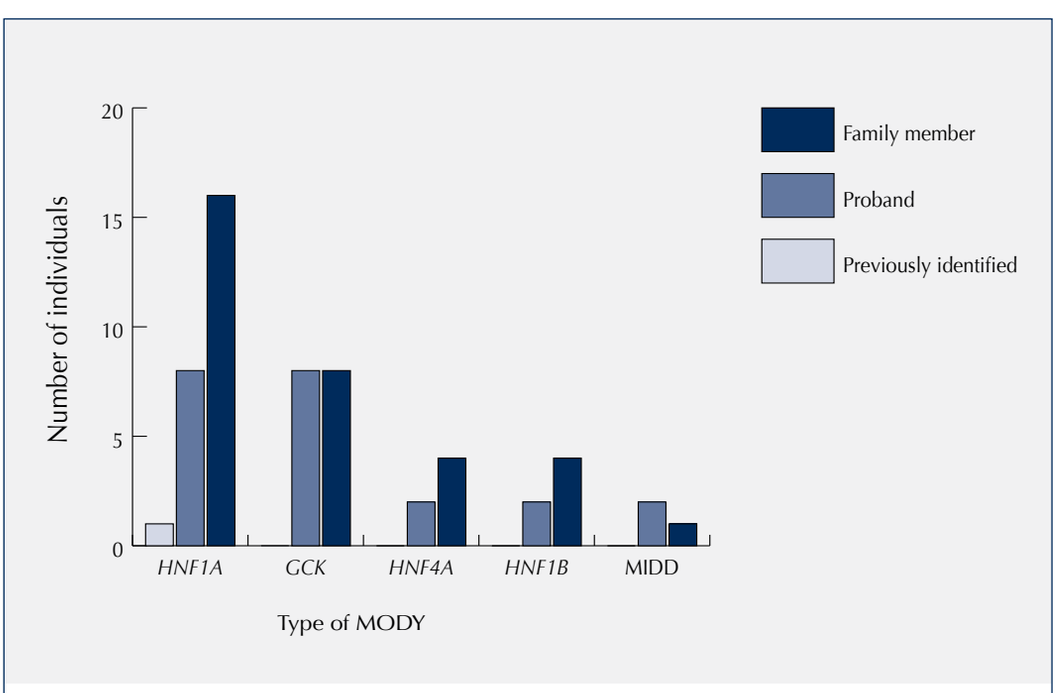

Figure 1. Individuals with monogenic diabetes in Brighton and Hove. Cases are shown by gene mutation. MIDD= mitochondrial diabetes and deafness; MODY= maturity-onset diabetes of the young

48 referred) and 32 family members. Twenty-three (42.5%) have *HNF1A* MODY, 16 (30%) have *glucokinase* (*GCK*) MODY, six (11%) have *HNF4A* MODY, six (11%) have *HNF1B* MODY and three (5.5%) have mitochondrial diabetes and deafness (MIDD) (*Figure 1*). At time of genetic testing, the people were on a wide range of therapies, including diet only, a combination of oral hypoglycaemic agents and insulin, and insulin alone. As a result of a positive genetic test for MODY, 11 people (with *HNF1A*, *HNF4A* and *GCK*) were able to discontinue their insulin treatment.

Only four out of the 21 people with *HNF1A* MODY and two out of six people with *HNF4A* MODY were on a sulphonylurea at the time of genetic testing, which is considered the optimal first-line treatment for *HNF1A* and *HNF4A* MODY in these cases (Pearson et al, 2003; Hattersley, 2005). Once a genetic diagnosis had been made, sulphonylureas were added in 12 out of 21 cases of *HNF1A* MODY and in two out of six cases of *HNF4A* MODY.

Of the 16 patients diagnosed with *GCK* MODY, seven were not on any treatment, as recommended (Stride and Hattersley, 2002; Hattersley, 2005) and nine were treated with an oral hypoglycaemic agent or insulin at time of testing. After genetic diagnosis, seven out of the nine people were able to discontinue their previous treatment.

People with *HNF1B* MODY and MIDD typically require insulin treatment (Stride and Hattersley 2002; Hattersley 2005). Four people with *HNF1B* mutations and diabetes were on insulin prior to genetic testing, and following testing one person previously on no medication commenced insulin. One individual with MIDD was treated with insulin at time of testing and remained on insulin post diagnosis; the other was on oral hypoglycaemic agents initially but was subsequently transferred to insulin once the diagnosis of MIDD was made.

The total of 54 people identified with confirmed monogenic diabetes within the Brighton and Hove area since genetic testing was available gives a population prevalence of 1 in 5000 or 200 cases per million (based on a population of 273 369 from 2011 UK Census data [Office for National Statistics, 2012]).

Monogenic clinic

A monogenic clinic was set up at the Royal Sussex County Hospital in 2008 to provide a specialist service for those with, or currently under investigation for, monogenic diabetes. This is run by the GDN, consultant physician and specialist dietitian, all of whom have attended training in monogenic diabetes in Exeter. The clinic is held fortnightly and approximately eight people attend each clinic; this includes more than 20 people with confirmed monogenic diabetes from neighbouring districts. This clinic provides the opportunity for these individuals to be reviewed by a team with high levels of knowledge of monogenic diabetes and ensures that other family members with diabetes are also offered genetic testing. The possibility of predictive genetic testing can also be discussed with "unaffected" family members.

Discussion

Whilst the training and commitment required to be GDN may mean it is not be possible for everyone involved in diabetes care, incorporating simple strategies into diabetes clinical care can help identify potential people with monogenic diabetes. These individuals may have been attending diabetes services for many years with an incorrect diagnosis. Such strategies include considering further investigation of those diagnosed before 25 years of age with an affected parent, or any individual diagnosed below 6–9 months of age. Results of non-genetic tests (such as UCPCR and pancreatic antibodies) can be interpreted by the GDN and use of the online MODY probability calculator, available at http://bit.ly/12ssrnJ (Shields et al, 2011) can ensure only those people with a reasonable probability of monogenic diabetes are referred for genetic testing.

The GDNs recognise that there may be a delay between the delivery of presentations on monogenic diabetes, the referral and the confirmation of a molecular genetic diagnosis in the individual and other family members. However, the satisfaction of confirming the correct diagnosis and the ensuing changes to treatment are highly motivating for all members of the diabetes team. An example of this in the

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team in Brighton and Hove was an individual identified by a retinal screener, who was subsequently confirmed to have *HNF1A* MODY and consequently was able to stop long-term insulin.

Conclusion

Establishing a GDN post in East Sussex led to the identification of an additional 54 people with monogenic diabetes within Brighton and Hove. Prior to the association with the GDN project and the Exeter monogenic diabetes team, the prominence of monogenic diabetes within the acute diabetes service in Brighton mirrored that of many diabetes services across the UK. Whilst this training required time and commitment, it proved invaluable in increasing confidence in monogenic diabetes. Local healthcare professionals have also become more aware of questioning the "documented" diagnosis and family history of those with young-onset diabetes. There has been a substantial increase in the use of pancreatic antibody and UCPCR testing to aid differential diagnosis within the area.

Exposure to specific, intensive training regarding the genetics, clinical care and treatment of monogenic diabetes enabled the development of the monogenic diabetes service at the Royal Sussex County Hospital. This service attracts referrals from beyond the immediate diabetes clinical community, resulting in additional revenue from outside the locality. Assessment of clinical features and family history is critical in the detection of monogenic diabetes. People diagnosed before 25 years with an affected parent (particularly those who are "negative" to pancreatic antibodies and UCPCR positive more than five years post diagnosis) should be referred to their local GDN or the Exeter team for genetic testing. ■

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To find out more about monogenic diabetes or to contact your local Genetic Diabetes Nurse and monogenic clinic please visit www.diabetesgenes.org

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