The search for undiagnosed MODY patients: what is the next step?

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Abbreviation

PNDM permanent neonatal diabetes

When, more than two decades ago, I started working as a physician providing medical care to patients with diabetes, I was completely unaware of the diversity of its forms. At that time, I knew only that there was an insulin-dependent diabetes (renamed later as type 1) and a non-insulin-dependent diabetes (currently known as type 2). I am convinced that this was the predominant viewpoint at that time. Over the last 20 years, however, scientists—both basic researchers and clinicians—have discovered and characterised more than 20 forms of monogenic diabetes [1–3]. The term MODY attracted my attention in the early 1990s when discoveries of its molecular basis were emerging [4, 5] and my personal interest in the genetics of diabetes was growing. It should be noted that much earlier there were

some bright physicians whose brilliant observations pointed to rare cases of patients with diabetes who have a very rich family history of this disease and whose symptoms did not fit into either of the two categories identified at that time [6, 7]. These patients shared some common features, such as an autosomal dominant inheritance and abnormalities of insulin secretion; they were also usually thin and non-insulin-dependent. We later learnt that MODY was not a uniform entity but, rather, constituted a heterogeneous group that included several forms of single gene diabetes [8, 9]. Clinically, patients with MODY exhibited different degrees of hyperglycaemia, rates of disease progression, responses to pharmacological treatment and concomitant extra-pancreatic features. Individuals involved in MODY research revealed the origin of these differences and learnt how to use them in medical practice [2, 10–12]. Although the molecular aetiology of MODY has not yet been fully dissected, genetic testing is now available for the most prevalent subtypes.

To date, thousands of MODY patients have been diagnosed all over the world, most of them probably thanks to research projects. These individuals, along with their families, benefited from genetic testing. Many patients, mainly carriers of the *HNF1A* mutation, were able to switch from insulin to sulfonylurea [13, 14]. Not only did their glycaemic control improve [14], but it is likely this switch also enhanced their quality of life. Some other patients, mostly individuals with *GCK* mutations, were able to discontinue pharmacological treatment altogether and controlled their diabetes through diet alone [15]. The genetic diagnosis also defined the prognosis for the disease progression or, in predictive testing, the risk of diabetes development in the examined individuals and their relatives. One may assume, although this has yet to be

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objectively proven on a large patient population, that the cost of their medical care was reduced as a result of treatment optimisation and decreased use of glucometric strips and reduced number of referrals for laboratory tests (type 1 diabetes related auto-antibodies, insulin levels etc.) [15]. However, solid health economic analysis is lacking in this area; this is why we only have a ballpark cost for genetic testing in Europe. Nevertheless, there can be no doubt that all of us—patients, healthcare providers and entire societies—benefit from the changes in clinical practice that have resulted from genetic discoveries. We currently need to answer a few important questions: How many MODY patients are there estimated to be in European countries? How many of them have yet to be diagnosed? Once these questions have been answered, the next task will be to find a way of identifying most, if not all, MODY patients and to provide them with optimal medical care. In other words, we need to abandon the narrow perspective of local research centres and start perceiving MODY diagnosis as part of routine clinical practice. Obviously, we must not forget about the necessity of pursuing well-organised genomic research focused on the unelucidated MODY cases and finding new genes.

In this edition of *Diabetologia*, Shields et al. report on their efforts to answer the above-mentioned crucial questions concerning the prevalence of MODY [16]. There has been some earlier experience with other monogenic forms of diabetes, such as permanent neonatal diabetes (PNDM). For example, it has been reported that PNDM occurs at least once in 260,000 live births [17]. Unlike MODY, PNDM has a strict and simple definition: diabetes diagnosed before the end of the sixth month of life. In addition, the task of determining the incidence PNDM was facilitated by registries of juvenile diabetes, which are available in some countries [18]. With MODY, however, the challenge is much more difficult as we cannot give it a precise definition. The main reasons being that age at diabetes diagnosis spans a wide range and that the clinical picture frequently overlaps with more common forms of this disease. Based on the number of identified mutation carriers in the UK (1,177 individuals between 1996 and 2009) and their distribution throughout the country, British scientists estimated the minimum prevalence of MODY to be 108 cases per million population [16]. This means that, in the UK alone, there are at least 5,000 individuals with undiagnosed MODY. We may cautiously assume that the actual number is several times higher, probably reaching a rate of approximately 1% of all diabetes cases. This notion is supported by data from earlier, but much smaller, studies [19, 20]. If these figures are extrapolated to the entire population of Europe, the number of MODY patients waiting to be diagnosed may go into hundreds of

thousands, and the number of genetic tests that need to be performed, taking into account the pick-up rate for the probands described in the commented paper, is several times larger and is expressed in millions! Thus, not only is there a job to do in the UK, but other European countries have an even longer way to go. For example, in Poland, a country with a population of 38 million, with several scientific groups committed to MODY research for over a decade, the number of identified patients is about 300 (M. T. Malecki, W. Mlynarski, unpublished data). How can we rise to the challenge of identifying the remaining as yet undiagnosed MODY patients?

The paper by Shields and colleagues provides some clues [16]. There is marked regional variation in the prevalence of identified MODY cases in the UK. Therefore, attention should be focused on the areas where the referral and diagnosis rates are the highest. South West England is one such area. The high number of diagnosed MODY cases in this area can certainly be explained by the influence of a world-leading research centre in the field of monogenic diabetes, based in the Peninsula Medical School. This centre, which also offers intensive education for physicians and nurses in the diagnosis of MODY, must have locally increased the awareness of MODY and the importance of the differential diagnosis of diabetes. Another region with a high number of confirmed cases is Scotland. Interestingly, this is the only area in the UK where central funding for genetic testing is provided. So it seems that to successfully identify MODY patients, an awareness among physicians and nurses is needed as well as available funds to perform screening. To maximise the medical and economic effectiveness of the screening, appropriate guidelines are required and these are already available [21]. Is there anything apart from education and money that may help the search for MODY patients? Two tools should be mentioned here. The first is new generation sequencing, which, when introduced to genetics labs, will substantially boost the efficacy of screening and will hopefully reduce its cost [22]. The second is the development of cheap, non-genetic biomarkers that are widely available and can be used as a more economical screening test to perform pre-diagnostic molecular testing [23]. Such testing could possibly be combined with phenotypic, clinical or other laboratory information. Over the last decade several such biomarkers were proposed, for example apolipoprotein M or 1,5-anhydroglucitol for *HNF1A* MODY [24, 25]. The enthusiasm concerning their clinical usefulness after the initial publications was, however, reduced [26], or even perished [27, 28], following the results of replication studies. Thus, we should not expect that any of these earlier candidate biomarkers will be used in clinical practice. Nevertheless, the search for new biomarkers is underway and has been

facilitated by the European Union funding the international Collaborative European Effort to Develop Diabetes Diagnostics (CEED3; www.metabol.cm-uj.krakow.pl/ceed3/eng.htm) scientific consortium, which aims to identify these markers.

So, returning to the initial question asked by Shields et al.: How many MODY cases are we missing? We know that we are missing most of them but we are also aware of how to search for them and, even more importantly, what to do once they are found.

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