PERSPECTIVE

The rare must become common

It is important to raise awareness of rare diseases if the high cost of delayed diagnosis is to be brought down, says **Marc C. Patterson**.

Lysosomal storage disorders (LSDs) — like other rare diseases — are often not diagnosed until long after symptoms have appeared. The average delay in diagnosing Niemann–Pick type C, for instance, is about five years[1], but individuals with LSDs may be undiagnosed for decades[2].

A delay in diagnosis carries heavy costs. First, it extends an expensive and emotionally exhausting diagnostic odyssey that might include multiple diagnostic tests, missed time at work for carers, and repeated travel to distant medical facilities. Second, parents who are unaware that their child has the disorder cannot make informed decisions regarding the risk of having more children who might be affected. And finally, any delay in starting treatment risks irreversible tissue injury and loss of cells, particularly neurons.

One might argue that it is difficult for any physician to be aware of every rare disease. However, although LSDs are individually rare, together they are reasonably common, so it is highly likely that a clinician will encounter at least one in his or her career. The conventional response has been to educate health-care workers to recognize the early symptoms of LSDs. Specific algorithms can assist in identifying patients, but the clinician must first think of the disorder in order to use the tools. Given the vast array of disorders and symptoms, this is an unrealistic expectation, particularly in a busy primary practice. A better approach may be to harness the power of the Internet. Freely available online tools can create differential diagnoses[3], although broad access to such tools has its downsides. They may help to reinforce the concerns of the worried well, for example, leading to unnecessary investigations.

But even if the information is available, a physician cannot make a diagnosis until after the disease manifests. And the appearance of symptoms implies that the reserve capacities of the affected organs has already been exhausted — often irreversibly.

It is possible to identify asymptomatic individuals by population screening, typically in newborns. Several advocacy groups have promoted this approach in the United States with some success. But screening for LSDs is a complex undertaking that goes far beyond the technical challenge of simply adding another assay to the panel of tests. Positive screens must be rapidly confirmed with definitive assays, and families must be quickly informed of results — and offered counselling and follow-up. These services may be considerably more expensive than the cost of testing alone. And there is no certainty that a positive screen correlates with early infantile disease. Families of children who are positively identified as having an LSD, but who have not yet displayed disease progression, have to live with this uncertainty and the necessity for lifelong monitoring (see page S162).

As an alternative, screening potential parents for carriers provides the opportunity to prevent the disease in the first place. If both partners screen positive, they have several options: abstain from having children together; obtain a preimplantation diagnosis; or terminate an affected pregnancy. Screening carriers has been used to prevent Tay–Sachs disease in the Ashkenazi Jewish population over the past few decades[4]. The incidence used to be 1 in 2,500 births, but it has fallen by more than 90% since screening was widely implemented. Several factors have contributed to this outcome: the carrier frequency is high (around 1 in 25 in the at-risk population, compared with 1 in 250 in the general population); an accurate blood test is available; and the communities rolled out an effective education programme in schools and places of worship, achieving almost complete participation. Such circumstances do not exist for most LSDs, although advances in genetic sequencing will make it easier to identify LSD carriers and aid primary prevention[5].

There is no single solution to the problem of delayed diagnosis in lysosomal disorders, but it is clear that progress presents more of an engineering challenge than one of individual initiative and knowledge. Such systemic solutions have been effective in improving quality in industry, but medicine has been slow to adopt them. The approach that is most likely to improve early diagnosis is screening newborns, which is already well established worldwide for other conditions. If reliable screening tests can be developed, the next step is to persuade governments to add LSDs to their screening panels. In the United States, this must be done on a state-by-state basis. Advocacy groups, in collaboration with medical professionals, have been quite effective in getting this done, albeit in only a handful of states so far. In countries with national health systems, a centralized approach will be possible. Programmes will need to be adequately funded with rapidly accessible resources for counselling, and follow-up must be integral to the programme and the population in general. And medical professionals must be educated about the benefits and risks of screening.

SCREENING CARRIERS IS THE MOST **DESIRABLE MEANS** OF ELIMINATING THESE DISEASES IN THE **LONG TERM.**

Screening carriers is the most desirable means of eliminating these diseases in the long term, but the considerable technical challenges of cheaply sequencing and interpreting DNA must first be solved. In addition, a public that is wary of government interventions and fearful of the power of the new genetics will have to be persuaded that the benefits of eliminating these devastating diseases outweigh the perceived risks to privacy and peace of mind. ■

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