Paediatric evaluation for inherited conditions: how do we investigate?

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This editorial refers to ‘Sudden cardiac death: clinical evaluation of paediatric family members’ by M. Tomaske et al., on page 421.

The importance of cardiological evaluation of families following sudden unexplained death (SUD) or diagnosis of an inherited cardiac condition (ICC) has been long established.1–3 The additional value of genetic testing, in the context of a likely ICC, is also recognized.4,5 Tomaske et al.6 report on their experience of paediatric investigation for ICCs. Their study cohort consists of a heterogeneous population referred consecutively to a tertiary centre over a 5-year period. Paediatric blood relatives with known familial ICC or SUD were included. The authors devised an investigational protocol, with an electrocardiogram (ECG), 24 h Holter monitoring, and echocardiogram in the first instance, followed by signal-averaged ECG, an event recorder, and cardiac magnetic resonance imaging as required. Mutation analysis followed upon the demonstration of a cardiac channelopathy phenotype. This offers an opportunity to compare diagnostic yields in evaluation focused on paediatric subjects with that of previously reported predominantly adult groups.

A disease prevalence of 39% was demonstrated among children in whose families an ICC was already confirmed, providing a compelling argument for the investigation of these children, even when asymptomatic. This reflects the autosomal dominant inheritance of the ICCs encountered, diluted by the investigation of non-first-degree relatives referred due to anxiety in a family. Hence, in affected families, where disease-causing mutations are not identified and cannot guide their assessment, it is incumbent upon physicians to offer cardiological evaluation of children.

Among SUD families, where investigation of adult relatives was non-diagnostic or where no adult relatives were referred for evaluation, paediatric cardiological evaluation is supported by a diagnostic yield of 20%. This compares favourably with existing data in families with predominantly adult members and supports the evaluation of children, even when the index case’s first presenting symptom was sudden death in adulthood.

Sudden death risk in paediatric relatives

The critical importance of paediatric investigation is highlighted by the finding of potentially life-saving appropriate implantable cardioverter-defibrillator (ICD) discharges in four patients treated following their evaluation. There was zero mortality over a mean follow-up period of 3.6 years. Furthermore, among the 13 SUD families, one appropriate ICD discharge was recorded in a patient diagnosed with short QT syndrome. One must, however, take into account the potential risk of device therapy in children, particularly with regard to lead problems and inappropriate shocks.7

Limitations in identification of paediatric disease

Variable and age-related penetrance of ICCs in adults is an established phenomenon,8 and the difficulties encountered in assessing phenotypes are compounded in children. As acknowledged by the authors, Brugada syndrome, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) can often only be diagnosed following either exertional or drug provocation.4,9,10 Thus, the absence of exercise, ajmaline, and epinephrine testing in the authors’ protocol may have reduced the diagnostic yield. This is underpinned by the lack of CPVT and Brugada syndrome diagnoses in SUD families, in contrast to other similar populations.2,3 Two children with familial hypertrophic cardiomyopathy were diagnosed 2 to 3 years after initial evaluation, demonstrating age-related penetrance and mandating serial follow-up until adulthood in this context.

In this cohort, genetic testing was only utilized following the detection of ion channel disease within the family. This therefore limits the potential for genetic diagnosis in cardiomyopathies and may have further compromised the diagnostic yield. A potential role for molecular autopsy, or comprehensive molecular analysis,
following SUD has been described,⁴ which, if available, may have supplemented the diagnostic yield in the cohort.

A familial approach

Although Tomaske et al.⁶ have established a worthwhile diagnostic yield in a paediatric referral population, the question of how best to configure a clinical service remains. Given that this cohort represents consecutive referrals, it is important to note that at least four (22%) of the affected children diagnosed in their clinic were initially referred following adult familial evaluation. This may represent an opportunity for more holistic service provision as a combined adult and paediatric cardiological evaluation would offer multiple potential benefits: shorter time to paediatric evaluation, better communication of familial results, simpler assessment of significance of borderline results, and possibly increased diagnostic yield.

Conclusions

In conclusion, paediatric evaluation is a vital component of the investigation of SUD and ICCs, and Tomaske et al. demonstrate this. It diagnoses disease that is treatable, although the risk of ICD therapy in children is not unappreciable. This evaluation should encompass a comprehensive range of investigations including genetic testing in the context of a joint adult and paediatric service. Provocation testing appears likely to increase the diagnostic yield in SUD families, but further evidence focused on a paediatric population is required. Molecular autopsy may also play an important role.

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References