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Early genetic diagnosis in neonatal diabetes a ‘new framework for clinical care’

Published on October 1, 2015 at 9:15 AM

By Eleanor McDermid, Senior medwireNews Reporter

Early genetic testing of babies with suspected neonatal diabetes identifies the underlying cause in more than 80% of cases, say researchers.

“[O]ur study describes the transformation that can occur in clinical practice once genetic testing becomes the initial investigation”, write Andrew Hattersley (University of Exeter Medical School, UK) and study co-authors.

They report data for 1020 patients, from 79 countries, referred for Sanger sequencing at the Exeter Molecular Genetics laboratory, which provides free testing for neonatal diabetes. Patients referred after 2012 also had comprehensive testing with the targeted next-generation sequencing assay.

The findings show a shift towards earlier testing, with the time between clinical diagnosis and genetic testing falling from 4 years in 2004 to less than 3 months between 2012 and the study end in August 2013.

Furthermore, patients referred early after diagnosis were often tested before clinical characteristics of their condition had fully developed. For example, only 12% of patients with Wolcott-Rallison syndrome referred within 3 months of clinical diagnosis had developed nondiabetic features such as skeletal dysplasia, compared with 83% of those with a delay of more than 48 months.

“The future of care in neonatal diabetes will increasingly rely on the results of genetic testing with the genetic diagnosis, not only informing a clinician of the likely course and best treatment for the diabetes, but also predicting development of additional clinical features”, write the researchers in *The Lancet*.

The proportion of patients with an unidentified cause of their diabetes was similar regardless of whether their parents were consanguineous or non-consanguineous, at 15% and 18%, respectively, suggesting “that both dominant and recessive causes of neonatal diabetes are still undiscovered”, say Hattersley et al.

However, consanguinity did affect the cause of diabetes; mutations in *KCNJ11* and *ABCC8* were the two most common causes in children of non-consanguineous parents, accounting for 46% of cases, whereas the most common finding in children of consanguineous parents was Wolcott-Rallison syndrome arising from a mutation in *EIF2AK3*, which occurred in 24% of cases.

The team identified 50 patients whose condition required pancreatic enzyme replacement, seven whose diabetes could potentially be treated with thiamine, and 184 who were likely to develop neurological abnormalities.

“This represents a new framework for clinical care in neonatal diabetes, with genetic diagnosis often preceding development of clinical features and guiding clinical management”, they say.

In an accompanying commentary, Leif Groop (Lund University, Malmö, Sweden) notes that current testing requires pre-identification of the likely culprit genes, which is not appropriate for the minority of cases that are not clear cut.

“The next step in less clear clinical situations will be whole-genome sequencing without any assumptions about what genes might be involved”, he says. “Although cost is a restriction in this situation, this whole-genome sequencing approach can already work for recessive mutations, which are rare.”

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