Pectus Excavatum Is Part of the Clinical Spectrum of HNF1B MODY5

Danièle Dubois-Laforgue,[1] Christine Bellanné-Chantelot,[2] Jean-François Subra,[3] and José Timsit[1]

Diabetes Care 2014;37:e72–e73 | DOI: 10.2337/dc13-2822

HNF1B maturity-onset diabetes of the young (MODY) (previously named MODY5) is a syndrome due to heterozygous molecular anomalies of the hepatocyte nuclear factor (HNF)1B that may associate diabetes, morphological and functional abnormalities of the kidneys and of the pancreas, liver test anomalies, and genital tract malformations (1,2). MODY5 is due to *HNF1B* point mutations in half the cases, and is associated to a chromosome 17q12 deletion encompassing the *HNF1B* gene in the other half (3,4).

Pectus excavatum (PE) is the most frequent anterior chest wall deformity. It has been described as an isolated anomaly or as part of many genetic syndromes, including monogenic diseases and chromosome aberrations (reviewed in 5). So far, PE has not been described in the context of *HNF1B* anomalies.

Following the observation of a patient with typical MODY5 and PE (case 1, Table 1), we have reviewed the files of 59 adult patients (29 males, 30 females) with an *HNF1B* molecular anomaly (31 mutations, 28 deletions). In six patients, the presence of PE was mentioned by the referring physician (including a father and his son, cases 1 and 2), and was confirmed by two of us. No patient had a severe form with respiratory or other clinical consequences. The main characteristics of the six patients are shown in Table 1. Diabetes, present in five of six patients, was revealed by acute onset in three patients. Basal and glucagon-stimulated C-peptide concentrations were low in the five tested patients. In the sixth patient, follow-up fasting blood glucose and HbA_{1c} were 5.7 mmol/L and 34 mmol/mol, respectively. Renal disease was present in all patients. Liver tests abnormalities were observed in five of six patients, with fluctuating increased levels of transaminases and/or γ-glutamyl transferase. Fecal elastase concentration was decreased in three of five tested patients.

In this series of MODY5 patients, the minimal prevalence of PE was 10% (8% in probands, and 21% in male patients). Since chest wall morphology was not systematically described in the files, the actual frequency could be higher. Nevertheless, the observed prevalence is by far much higher than that expected in the general population, which has been reported to be 1:400, with a male-to-female ratio of 4:1 (5).

Among the six patients with MODY5 and PE, an *HNF1B* point mutation was found in four patients (three probands) and an *HNF1B* deletion in two patients (Table 1). These results suggest that molecular anomalies of the *HNF1B* gene may be involved in the development of PE, and expand the clinical spectrum of the HNF1B-associated disease. The presence of PE may strengthen the suspicion of MODY5 in some patients with uncommon forms of diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. D.D.-L. and J.T. researched data and wrote the manuscript. C.B.-C. and J.-F.S. researched data and contributed to discussion. J.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Bellanné-Chantelot C, Chauveau D, Gautier JF, et al. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med 2004;140:510–517
2. Chen YZ, Gao Q, Zhao XZ, et al. Systematic review of *TCF2* anomalies in renal cysts and diabetes syndrome/maturity onset diabetes of the young type 5. Chin Med J (Engl) 2010; 123:3326–3333
3. Bellanné-Chantelot C, Clauin S, Chauveau D, et al. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. Diabetes 2005;54:3126–3132

[1]*Department of Diabetology, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris and Université Paris Descartes, Paris, France*
[2]*Department of Genetics, Hôpitaux Universitaires Pitié-Salpétrière–Charles Foix, Assistance Publique-Hôpitaux de Paris and Université Pierre et Marie Curie, Paris, France*
[3]*Department of Nephrology, Angers University Hospital, Angers, France*

Corresponding author: Danièle Dubois-Laforgue, daniele.dubois@cch.aphp.fr.

4. Ulinski T, Lescure S, Beaufils S, et al. Renal phenotypes related to hepatocyte nuclear factor-1β (*TCF2*) mutations in a pediatric cohort. J Am Soc Nephrol 2006;17:497–503

5. Kotzot D, Schwabegger AH. Etiology of chest wall deformities—a genetic review for the treating physician. J Pediatr Surg 2009;44: 2004–2011

Table 1—Main characteristics of six patients with *HNF1B* molecular anomaly and PE

Case #	Age (years)/sex	*HNF1B* molecular anomaly	Age at diabetes diagnosis (years)	Blood glucose at diabetes diagnosis (mmol/L)	HbA_{1c} at diabetes diagnosis (mmol/mol)	Diabetes treatment	Age at kidney disease diagnosis (years)	Renal cysts	Current GFR (mL/min/1.73 m^2)	Liver tests	Pancreas morphology
1	45/M	c.884G>A, R295H	24	22.2	122	Insulin	28	Yes	51	Cholestasis, cytolysis	Complete atrophy
2	22/M	c.884G>A, R295H	0.9	52.8	68	Insulin	Neonatal	Yes	87	Cholestasis	Atrophy body and tail
3	46/M	*HNF1B* deletion	23	19	130	Insulin	14	Yes	71	Cholestasis, cytolysis	Normal
4	43/M	c.143delT, L48fs	29	7.1	44	Insulin	26	Yes	28	Cholestasis, cytolysis	Ring pancreas
5	44/M	c.544+4A>C	44	7.5	50	Diet	42	No	58	Normal	Multiple microcalcifications
6	24/M	*HNF1B* deletion	No diabetes	NR	NR	NR	2	Yes	102	Cholestasis, cytolysis	Normal

GFR, glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula; M, male; NR, not relevant.