Intellectual disability in patients with MODY due to hepatocyte nuclear factor 1B (HNF1B) molecular defects


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1. Introduction

Intellectual disability (ID) is characterized by impairments of general mental abilities that have an impact on adaptive functioning in conceptual, social and practical areas, and which begin in the developmental period [1]. It affects 1–3% of the general population [2]. Chromosomal aberrations or mutations in almost 500 genes have been associated with ID. Among these genes, several are also involved in diseases with phenotypes that may overlap with ID, such as autism spectrum disorders (ASD) and schizophrenia.

Molecular defects of the hepatocyte nuclear factor 1B (HNF1B) have been associated with a syndrome that includes maturity-onset diabetes of the young 5 (MODY5 or HNF1B–MODY), kidney structural abnormalities, progressive renal failure, pancreatic hypoplasia and exocrine dysfunction, abnormal liver tests and genital tract abnormalities [3]. In half the cases, the HNF1B-related syndrome is due to HNF1B heterozygous mutations whereas, in the others, it is associated with HNF1B whole-gene deletion [3]. In all cases examined thus far, the latter results from a 17q12 deletion of 1.4–2.1 Mb, encompassing 20 genes including HNF1B [3–6].

Autism and/or ID have been described in patients with various HNF1B-related phenotypes, such as HNF1B–MODY [7], cystic kidney disease [4,8,9] and müllerian aplasia [10], always in the context of 17q12 deletion. On the other hand, in a large population study, the 17q12 deletion was recognized as a strong risk factor for ID, ASD and schizophrenia, being identified in 1/1000 of children referred for those conditions [11].

Whether the neurocognitive phenotypes associated with the 17q12 deletion result from deletion of HNF1B itself or another deleted gene, or from a contiguous gene syndrome, remains unknown [4,8,11].

To investigate the role of HNF1B abnormalities in the occurrence of cognitive defects, the frequency of ID was assessed according to the presence of HNF1B mutations or deletion in a large cohort of adult patients with HNF1B–MODY.

2. Research design and methods

The study population consisted of 107 adult patients with diabetes in whom a molecular abnormality of HNF1B had been identified, as described elsewhere [3]. The phenotype of the HNF1B-related syndrome was assessed through a questionnaire, filled in by referring physicians, that comprised clinical, biological and morphological items. ID was defined as limitations in intellectual functioning and in adapting to environmental demands, beginning early in life, and was appraised by the need for educational support, protected work or assistance in daily activities, and by the social skills of the patients [1]. Learning disability (LD) was defined as persistent difficulties in reading, writing, or mathematical-reasoning skills [1].

Of these 107 patients, 14 had access to detailed evaluations by a geneticist and a neurologist who were blinded to the patient’s HNF1B genotype. In case of clinical suspicion of cognitive defects, the evaluation was completed by neuropsychological testing, including the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III), and by further testing of executive functions (Trail-Making Test), memory [84-item Battery of Memory Efficiency (BEM 84)] and visuospatial function [Rey Complex Figure Test and Recognition Trial (RCFT)]. In patients presenting with ID or LD, single-nucleotide polymorphism (SNP) array analyses were performed, using the HumanCytosNP-12 v2.1 array scanner and assay (Illumina, Inc., San Diego, CA, USA), after excluding fragile X syndrome. Results were analyzed with GenomeStudio software, version 3.1.6 (Illumina). All patients gave their written informed consent.

The frequency of ID was assessed in two control groups of adult patients with diabetes followed in our department: 339 consecutive patients with type 1 diabetes (T1D); and 227 patients presenting with phenotypes suggestive of MODY, including 31 glucokinase (GCK)–MODY, 42 HNF1α–MODY, 13 HNF4α–MODY, five ATP-binding cassette subfamily C member 8 (ABCC8)–MODY, two insulin (INS)–MODY and 134 genetically screened patients with no identifiable molecular aetiology (referred to as MODY-X).

Results are reported as means ± SD or as frequencies (%). Comparisons between groups were made by non-parametric tests or by Fisher’s exact test.
The main characteristics of the 107 patients are shown in Table 1. ID was reported in 15 (14 proband) patients (14%). LD was noticed in a further nine patients (Table S1; see supplementary material associated with the article online). Overall, cognitive defects were thus observed in 24/107 patients (22.4%). Common causes of ID were ruled out by the search for fragile X syndrome and SNP array analyses, which excluded other large genomic deletions in all tested patients.

The frequency of ID was significantly higher in HNF1B–MODY patients than in those with TID [8/339 (2.4%), OR: 5.9, 95% CI: 2.6–13.6; \( P < 10^{-4} \)], or in those with other monogenic diabetes or MODY-X [6/227 (2.6%), OR: 6.0, 95% CI: 2.3–16.0; \( P = 0.0002 \]).

HNF1B–MODY patients with or without ID were similar as regards gender, age at diabetes diagnosis, duration and treatment of diabetes, frequency and severity of renal disease, frequency of pancreatic morphological abnormalities and livertest abnormalities, and frequency of arterial hypertension and dyslipidaemia (Table 1). HbA1c levels at the time of the study were higher in the patients with ID (9.4 ± 3.0% vs 7.3 ± 1.4%; \( P = 0.005 \)).

Of the 15 patients presenting with ID, six had HNF1B coding mutations (three missense, two splicing defects, one deletion of exon 5) and nine had a whole-gene deletion (Table S1). Thus, the frequency of ID was not statistically different between patients with HNF1B mutation (11%) or deletion (17%; \( P = 0.42 \); Table 1).

### 4. Discussion

Our study showed that ID affects 14% of adult patients with HNF1B–MODY, which is higher than the 1–3% reported in the general population [2] and than the 2.4–2.6% observed in our two control groups of adult patients with other diabetes subtypes.

The main characteristics of the HNF1B–MODY patients with ID did not differ from those without ID, except for the poorer glycaemic control observed in the former.

In patients with HNF1B-related syndrome, the occurrence of cognitive defects has been noted almost exclusively in paediatric series. ID/ASD has been reported in two adolescents with renal cystic disease, livertest abnormalities and diabetes [7]; developmental delay and/or learning difficulties were quoted in three young patients presenting with multicycstic renal disease [8]; and speech delay in two children with renal cystic disease [9]. In a series of 86 children with HNF1B-related renal disease, three cases of ASD were noted [4]. The systematic evaluation of 28 children with HNF1B-associated kidney disease also suggested an increased risk of neuropsychological disorders in those harbouring the 17q12 deletion [5]. A recent study performed in a UK cohort reported the presence of neurodevelopmental disorders in eight out of 20 patients with renal abnormalities or diabetes due to HNF1B whole-gene deletion [6]. In all these reports, cognitive defects were observed in the context of the 17q12 deletion.

Conversely, the 17q12 deletion has also been reported in children evaluated for ID, beyond the setting of HNF1B-related syndrome. Indeed, an association between the deletion and cognitive defects has been confirmed in paediatric cases with no renal abnormalities [12,13]. In one population study, the 17q12 deletion was detected in 18/15,749 children referred for ASD and/or ID, but in none of the controls [11]. However, detailed phenotypes, available for nine children, were suggestive of the HNF1B-related syndrome, as all but one showed multicycstic renal disease and/or kidney morphological abnormalities, and one had diabetes. Altogether, these observations strongly suggest that cognitive defects are part of the phenotype associated with the 17q12 deletion.

Whether cognitive defects may result from molecular alterations of HNF1B itself remains unsolved. Learning difficulties...
have been reported in two patients with HNF1B frameshift mutations: one was a man with polycystic kidney disease [14]; the other was a woman with renal disease, diabetes, and liver tests abnormalities [15]. ID has also been reported in two patients with HNF1B-kidney disease due to point mutations [16]. However, in these four patients, a search for other causes of cognitive defects was not performed. In the above-mentioned UK study, no neurodevelopmental disorders were reported in 18 patients with intragenic HNF1B mutations [6]. Conversely, in our study, ID was observed in 6/54 patients (11%) with an HNF1B point mutation, a frequency three times greater than in the general population, and common causes of ID were ruled out in four of them. These discrepancies might be explained by the small number of patients \( n = 18 \) with HNF1B mutations in the UK study, and by the fact that neurocognitive phenotypes might be milder in patients with mutations.

Thus, our observations may suggest the involvement of HNF1B defects in the occurrence of cognitive defects in patients with HNF1B–MODY. The links between HNF1B molecular abnormalities and intellectual developmental disorders remain elusive. Nevertheless, it should be noted that HNF1B is one of the evolutionarily conserved genes involved in the hindbrain development of zebrafish and mice [17]. However, the role of HNF1B in the human brain has yet to be established.

In our study, because of geographical remoteness, only a small number of patients had access to detailed neurological evaluation. However, the absence of selection bias is supported by the similar spectrum of HNF1B-related syndrome in patients evaluated by either examination or questionnaire (Table S2; see supplementary material associated with the article online). Moreover, the accuracy of the diagnosis made by referring physicians—ID vs no ID—was confirmed in all patients who underwent neurological evaluations.

5. Conclusion

ID is more frequent in adults with HNF1B–MODY than in the general population or in patients with other diabetes subtypes. Moreover, it may affect patients with HNF1B point mutations as well as those with 17q12 deletion. Further studies are needed to refine the cognitive phenotypes of HNF1B-related syndrome and to precisely define the role of HNF1B itself in their occurrence.

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Disclosure of interest

The authors declare that they have no competing interest.

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### Appendix A. Supplementary data

Supplementary material (Tables S1 and S2) related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2016.10.003.

### References
