Autism in three patients with cystic or hyperechogenic kidneys and chromosome 17q12 deletion

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Abstract

Background. We report autism in 3 out of 53 children with cystic or hyperechogenic kidneys and heterozygous 17q12 region deletion encompassing hepatocyte nuclear factor-1beta (HNF1B).

Results. They presented mental retardation, social interaction impairments, verbal and non-verbal communication deficits and stereotyped behaviours. Deletion size and location of breakpoints were similar to those reported in patients with renal disease/diabetes only.

Conclusion. Reciprocal genomic rearrangements of the 17q12 region, reported in patients with mental retardation and epilepsy, could also be involved in autism. Nephrologists should be aware of the possibility of autism in patients with 17q12 deletion including HNF1B locus.

Keywords: 17q12 deletion; autism; cystic kidneys; HNF1B deletion; mental retardation

Introduction

Hepatocyte nuclear factor-1beta gene (HNF1B) molecular anomalies are responsible for one-third of hyperechogenic/cystic kidneys in children [1–6]. Point mutations were first reported [1,3], but deletion of the 17q12 region encompassing HNF1B represents two-thirds of molecular anomalies [2,4–7]. Renal cysts and diabetes syndrome (RCAD) [8], liver disease and genital malformations are frequent [1–3,6]. Neurodevelopment disorders are not known manifestations of HNF1B molecular anomalies, except for the recent description of two patients with mental retardation [9,10].

We report 3 out of 53 children with kidney disease and HNF1B deletion who had autism.

Case reports

The three patients were born from non-consanguineous healthy parents. Prenatal ultrasonographies detected cortical hyperechogenicity and/or cysts (<5 mm). Only Patient 1 had moderate renal failure and mild cholestasis at last follow-up (Table 1). They were noticed between the age of 2 and 6 months to have no interest for persons and objects, no smile response and delayed motor development. Subsequently, they displayed no ability to talk, answer to their names or establish eye contact. They were restless, with repetitive behaviours such as water games, touching circular objects or aligning toys without playing appropriately.

Diagnosis of autism

The three children had early onset developmental delay and social interaction impairments, verbal and non-verbal communication deficits and stereotyped behaviours, concordant with the diagnostic criteria for autism of the American Psychiatric Association [11]. They had above cut-off scores for autism on the Autism Diagnostic Interview-Revised (ADI-R). Communication developmental age and developmental quotient were severely impaired (Table 2).

Molecular analysis

HNF1B was screened by quantitative multiplex PCR amplification [2]. Deletion breakpoints were determined by SNP array analysis (Figure S1). LHX1 gene encoding Lim homeobox protein 1, located in the deleted 17q12 region, was screened by sequencing the five exons and flanking exon–intron regions in the 3 patients and 32 HNF1B patients with autism, 16 with HNF1B deletion and 16 with point mutations. The parents of the three pa-
Patients were investigated for HNF1B deletion. Informed written consent was obtained for all patients and parents. The three autistic patients had a heterozygous de novo HNF1B deletion. The size of the deleted 17q12 region ranged from 1.49 Mb in Patient 2 to 1.85 Mb in Patient 1 and Patient 3 (Figure S1). Proximal and distal breakpoints were located within segmental duplications (proximal, 31 500 000–31 900 000 bp; distal, 33 300 000–31 900 000 bp) and did not disrupt genes. The deleted region included 19 other genes. The two 1.8-Mb deletions did not include

<table>
<thead>
<tr>
<th>Table 1. Clinical phenotype in the three patients with HNF1B deletion</th>
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<tr>
<td><strong>Patient 1</strong></td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td><strong>Age at last examination (years)</strong></td>
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<tr>
<td><strong>Kidney</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>Renal ultrasonography</strong></td>
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<tr>
<td><strong>Serum creatinine (µmol/L)</strong></td>
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<tr>
<td><strong>Creatinine clearance&lt;sup&gt;b&lt;/sup&gt; (mL/min/1.73 m²)</strong></td>
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<tr>
<td><strong>Pancreas</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>Glycaemia&lt;sup&gt;c&lt;/sup&gt; (mm/L)</strong></td>
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<tr>
<td><strong>HbA1c (%)</strong></td>
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<tr>
<td><strong>Liver</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>AST/ALT/GGT&lt;sup&gt;d&lt;/sup&gt; (IU)</strong></td>
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<tr>
<td><strong>At birth</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td><strong>At last examination</strong></td>
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<td><strong>Growth</strong></td>
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US, ultrasonography; N, normal; ND, not documented; SDS, standard deviation score.
Conversion factor: serum creatinine in micromoles per litre to milligrammes per decilitre, × 0.0113.
<sup>a</sup>At last examination.
<sup>b</sup>Schwartz formula.
<sup>c</sup>Non-fasting.
<sup>d</sup>Normal values: AST, 5–45 IU; ALT, 5–45 IU; GGT, 7–25 IU.
<sup>e</sup>Weight, height and weeks (w) of gestational age.

The three autistic patients had a heterozygous de novo HNF1B deletion. The size of the deleted 17q12 region ranged from 1.49 Mb in Patient 2 to 1.85 Mb in Patient 1 and

<table>
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<th>Table 2. Developmental characteristics in the three autistic patients with HNF1B deletion</th>
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<tr>
<td><strong>Patient 1</strong></td>
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<tr>
<td><strong>Developmental characteristics</strong></td>
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<tr>
<td><strong>Age at notification</strong></td>
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<tr>
<td><strong>ADI-R scores (cut-off score)&lt;sup&gt;x&lt;/sup&gt;</strong></td>
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<tr>
<td><strong>Social interactions</strong></td>
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<tr>
<td><strong>Communication and language</strong></td>
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<td><strong>Restricted and repetitive behaviours</strong></td>
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<td><strong>Onset before age 3</strong></td>
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<tr>
<td><strong>Developmental quotient (Brunet-Lezine-R)&lt;sup&gt;y&lt;/sup&gt; (months)</strong></td>
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The diagnosis of autism was ascertained by the following:
<sup>x</sup>The ADI-R, a diagnostic algorithm for autism focused on social interactions, communication and language and restricted and repetitive behaviours. The diagnosis of autism is established when the scores in all three areas meet or exceed cut-off values, and onset of the disorder is before the age of 36 months. The cut-off score for the communication and language domain is 7 for non-verbal subjects and 8 for verbal subjects. For all subjects, the cut-off score is 10 for the social interaction domain, 3 for restricted and repetitive behaviours and 1 for abnormalities before the age of 3 [12].
<sup>y</sup>The evaluation of speech–language–communication and communication development age used the Early Social Communication Scales (children with developmental age from 6 to 30 months) [13] and the Reynell Scale (children 1–6 years old or developmentally delayed) [14]. These scales assess verbal comprehension and expressive language, two processes essential to language development.
<sup>x</sup>Weight, height and weeks (w) of gestational age.
additional genes compared to the 1.5-Mb deletion. The analysis of the SNPs genotyping of the three patients was done in comparison to the database of genomic variants (http://projects.tcag.ca/variation) [16]. No copy number variant absent from this database was found. No LHX1 mutation was revealed in the 3 children or the 32 control patients. Genetic screening for known causes of autism (Fragile X, tuberous sclerosis, 15q11.13 duplication and 2qter or 22qter deletion [17–20]) was negative.

Discussion

Our 3 patients belong to a cohort of 86 children with cystic kidneys and HNF1B molecular anomalies, of which 33 (39%) had point mutations and 53 (61%) had whole-gene deletion (Bellanne-Chantelot, unpublished data). The proportion of the 3 with autism out of 53 (5.6%) with HNF1B deletion is far superior to the 1/150–1/300 prevalence of autism in the paediatric population [17–20]. Therefore, the association we report may not be fortuitous. Of note, Raile et al. [10] recently reported that two out of five children with HNF1B deletion, diabetes, renal and liver disease had mental retardation. Mental retardation affected motor skills, verbal performance and social skills in one of them (Case 1), suggesting autism. The other (Case 4) was previously reported as having ‘behavioural abnormalities resembling autism’ [9].

Autistic children may be misdiagnosed as 70% suffer from mental retardation [17] and 20–25% from epilepsy [21].

Linkage studies in autism have identified several replicated susceptibility loci, including 2q24–2q31, 7q and 17q11–17q21 [20,22,23]. Reasons for autism in patients with HNF1B deletion are uncertain. Deletion size and breakpoint locations in our two patients with autism and the two with mental retardation [10] were similar to those reported in patients with RCAD or restricted renal phenotypes [2,6,24].

Larger deletions, spanning at least a region of 2.1 or 2.3 Mb, have been reported in two children with renal disease only (FR35 in [24]) or RCAD (DUK677 in [6]).

HNF1B plays an essential role in the zebrafish [25] and vertebrates [26,27] hindbrain development. Therefore, autism could be a consequence of HNF1B anomalies on neural development and function. The absence of mental problems in large cohorts of patients with HNF1B deletion is not in favour of this hypothesis [1–8].

Since the deleted region encompasses 19 genes in addition to HNF1B, another hypothesis was that some genetic anomaly in the non-deleted allele could be present in patients with neurologic involvement. An obvious candidate was LHX1, which is expressed in the mouse kidney and brain and involved in vertebrate nervous system development [28,29]. However, we did not identify LHX1 molecular anomalies in our three patients. Elsewhere, we could not exclude a modifier gene outside the deleted region which, combined with 17q12 rearrangement, may explain the extended phenotype [30].

Interestingly, neurological phenotypes, including mental retardation and epilepsy, have been reported in association with genomic rearrangements of the 17q12 region [24,30,31]. Most recently, Nagamani et al. [32] reported developmental delay, cognitive impairment and/or seizures in four children with cystic kidneys and 17q12 deletion and cognitive impairment and behavioural abnormalities in four patients with reciprocal duplications in 17q12. These observations and our report suggest that rearrangements of the 17q12 region can be involved in neurological phenotypes, including mental retardation, epilepsy and autism. These neurological phenotypes could be underestimated since these patients are generally followed up by nephrologists and/or diabetologists for adult cases who may not be aware of the variable expression of autism.

In conclusion, autism appears as a possible manifestation associated with HNF1B deletion. Autism and/or mental retardation should be investigated in a large cohort of patients with HNF1B anomalies to confirm our observations and document the exact incidence of autism in patients with 17q12 deletion. Nephrologists should be aware of this neurodevelopmental disease to refer patients to psychiatrists for diagnosis and treatment.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

Conflict of interest statement. None declared.

References

2. Bellannée-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
22. Costa e Silva JA. Autism, a brain developmental disorder: some new pathophysiologic and genetics findings. Metabolism 2008; 57: S40–S43

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