Nephrol Dial Transplant (2020) 1–11
doi: 10.1093/ndt/gfaa243

ndt
Nephrology Dialysis Transplantation

ORIGINAL ARTICLE

Treatment and long-term outcome in primary nephrogenic diabetes insipidus

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ABSTRACT

Background. Primary nephrogenic diabetes insipidus (NDI) is a rare disorder and little is known about treatment practices and long-term outcome.

Methods. Paediatric and adult nephrologists contacted through European professional organizations entered data in an online form.

Results. Data were collected on 315 patients (22 countries, male 84%, adults 35%). Mutation testing had been performed in 270 (86%); pathogenic variants were identified in 258 (96%). The median (range) age at diagnosis was 0.6 (0.0–60) years and at last follow-up 14.0 (0.1–70) years. In adults, height was normal with a mean (standard deviation) score of −0.39 (±1.0), yet there was increased prevalence of obesity (body mass index >30 kg/m^2; 41% versus 16% European average; $P < 0.001$). There was also increased prevalence of chronic kidney disease (CKD) Stage ≥2 in children (32%) and adults (48%). Evidence of flow uropathy was present in 38%. A higher proportion of children than adults (85% versus 54%; $P < 0.001$) received medications to reduce urine output. Patients ≥25 years were less likely to have a university degree than the European average (21% versus 35%; $P = 0.003$) but full-time employment was similar. Mental health problems, predominantly attention-deficit hyperactivity disorder (16%), were reported in 36% of patients.

Conclusion. This large NDI cohort shows an overall favourable outcome with normal adult height and only mild to moderate CKD in most. Yet, while full-time employment was similar to the European average, educational achievement was lower, and more than half had urological and/or mental health problems.

KEY LEARNING POINTS

What is already known about this subject?

- primary nephrogenic diabetes insipidus (NDI) is a rare inherited disorder of impaired urinary concentration;
- previous literature predominantly concerns case reports, paediatric single-centre cohorts or genetic aspects; and
- data are lacking on long-term outcome.

What this study adds?

- this is the largest cohort so far reported and inclusion of 110 adults up the age of 70 years provides important data on long-term outcome;
- final height is essentially normal and chronic kidney disease is mild in most; and
- there is a high prevalence of obesity, flow uropathy and mental health problems.

What impact this may have on practice or policy?

- this study provides unprecedented information on long-term outcome that directly informs the management and prognosis of patients with NDI.

Keywords: AQP2, AVPR2, chronic kidney disease, flow uropathy, nephrogenic diabetes insipidus

INTRODUCTION

Primary nephrogenic diabetes insipidus (NDI) is a rare inherited condition of impaired urinary concentration [1]. Two genes have been identified as causative for NDI: *AVPR2*, encoding Type 2 vasopressin receptor in the kidney, and *AQP2*, encoding the water channel expressed on the apical side of the principal cell in the collecting duct [1]. *AVPR2* variants are inherited in an X-linked recessive manner, whereas variants in *AQP2*, located on Chromosome 12, are typically inherited in an autosomal recessive pattern, with rare autosomal dominant cases reported [2]. *AVPR2*-related disease is roughly 10 times more frequent than *AQP2*. Consequently, the vast majority of patients with NDI are male. Patients typically present in the first year of life with failure-to-thrive and vomiting. An affected adult will typically void around 10–12 L of urine in 24 h. Reported complications include flow uropathy, associated with the large urine volumes, as well as impaired school performance and behavioural abnormalities, such as attention-deficit hyperactivity disorder (ADHD) [2].

Primary NDI is rare, with an estimated incidence of approximately 1 in 100 000, and the few data available on long-term outcome are mostly based on small single-centre cohorts. We performed a cross-sectional cohort study to gather information on kidney function, flow uropathy, auxology, mental health, education, employment and living arrangements in patients with primary NDI across all ages.

MATERIALS AND METHODS

Clinical data

An e-mail was sent to the membership of the European Reference Network for Rare Kidney Diseases, the European Renal Association – European Dialysis and Transplant Association and the European Society for Paediatric Nephrology (ESPN) through their respective working groups for inherited kidney diseases, inviting clinicians to provide data on patients with a clinical diagnosis of inherited NDI. The e-mail contained a link to an online data form that was open from 26 June to 31 August 2019.

A total of 27 questions were asked about demographics, auxology, treatment, kidney function and comorbidities, such as hydronephrosis, bladder dysfunction and mental health problems. A list of all questions is provided in the Supplementary data, Table S1.

In cases of missing information or if provided data points were noted to be outliers, corresponding clinicians were contacted via e-mail for completion and/or verification of data. Data were deemed adequate for analysis if fewer than five items were missing, and the information provided was confirmed by the responsible clinician (Supplementary data, Table S2).

We used the age of 18 years to separate the cohort into a paediatric and adult group. The only exception is estimated glomerular filtration rate (eGFR), as the 'Schwartz' formula is recommended up to the age of 20 years [3].

Genotype–phenotype analysis

For genotype–phenotype analysis, we divided the cohort according to the genetic information into the following four groups: (i) negative: no causative variants identified in *AVPR2* and *AQP2*; (ii) untested: genetic testing not performed or (iii) causative variant(s) had been identified in *AVPR2* or (iv) *AQP2*. We also separated between missense and predicted loss of function (pLoF, which includes nonsense, frameshift and splice site) variants.

Auxology

Height data were normalized and expressed as standard deviation score (SDS). For children, calculations were done according to World Health Organization (WHO) data [4, 5], while for adults, the US 2000 Centers for Disease Control growth charts [according to National Health and

Nutrition Survey (NHANES) data] were used [6]. Normal height was defined as a calculated SDS ≥ -2.00.

Paediatric weight data were normalized and expressed as SDS, also using the WHO data. The body mass index (BMI) was calculated and defined as underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9) or obese ($\geq$30.0 kg/m^2), according to standard convention [7].

Kidney function

The eGFR in adults (>20 years old) was calculated using the Modification of Diet in Renal Disease formula [3, 8]. For children (2–20 years), we used the modified 'Schwartz' formula [3]. Prevalence of chronic kidney disease (CKD) was calculated and expressed in Stages 1–5 according to Kidney Disease: Improving Global Outcomes guidelines [9]. For comparison with the NHANES III cohort [10], data from patients aged 20–60 years ($n = 76$) were used for subsequent analysis of CKD prevalence. As there were only seven patients >60 years old, meaningful comparison for that age group was not possible.

Psychosocial information

We used a published estimate of a 5% worldwide prevalence of ADHD, while European epidemiological data on educational attainment and employment were extracted from the EuroStat database [11–13]. Mental health disorders were classified according to DSM-5 criteria [14].

GDP per capita ($)

Gross domestic product (GDP) per capita was based data on from the World Bank [15]. For analysis, we defined a low and high subgroup based on a 15 000$/year cut-off, as it roughly divided the cohort in half.

Statistics

Analysis was done in IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA).

Kolmogorov–Smirnov test was performed to assess normality of the data. Data following a normal distribution were expressed as mean ± SD. Non-normally distributed data were expressed as median with either range or interquartile range (IQR). Statistical significance for categorical/dichotomous variables was performed with the Pearson Chi-squared test. The Student's *t*-test was used to compare the means between two groups of parametric data and one-way analysis of variance test for three or more different groups. Mann–Whitney U-test was used to compare mean ranks between dichotomous variables.

RESULTS

Demographic and genetic data

A total of 315 cases (from 22 countries, Supplementary data, Table S3) were available for final analysis. Gender distribution was as expected unequal with 266 (84%) males and 49 (16%) females (Figure 1A). Genetic analysis in the two known NDI genes had been performed in 270 cases (86%), and of these, 258 (96%) were found to have causative variants (*AVPR2* = 216 and *AQP2* = 42); 45 individuals had not been genetically tested (Figure 1B). A list of all reported variants is provided in the Supplementary data,

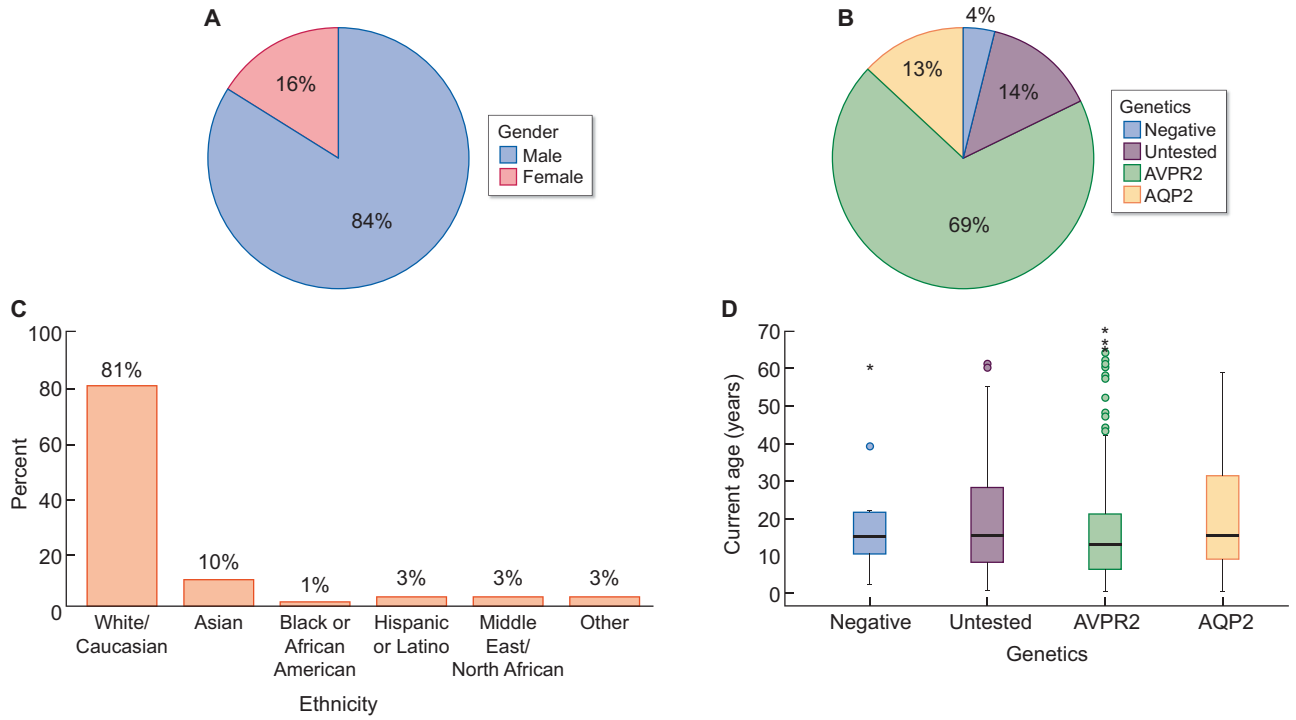

FIGURE 1: Demographic aspects of our cohort. Shown are selected characteristics of our cohort ($n = 315$, unless otherwise stated): (**A**) gender, (**B**) genetic group (for details see text) and (**C**) reported ethnicity ($n = 300$). (**D**) Boxplot graph detailing age at last follow-up according to genetic group [negative ($n = 12$), untested ($n = 45$), AVPR2 ($n = 216$) and AQP2 ($n = 42$)].

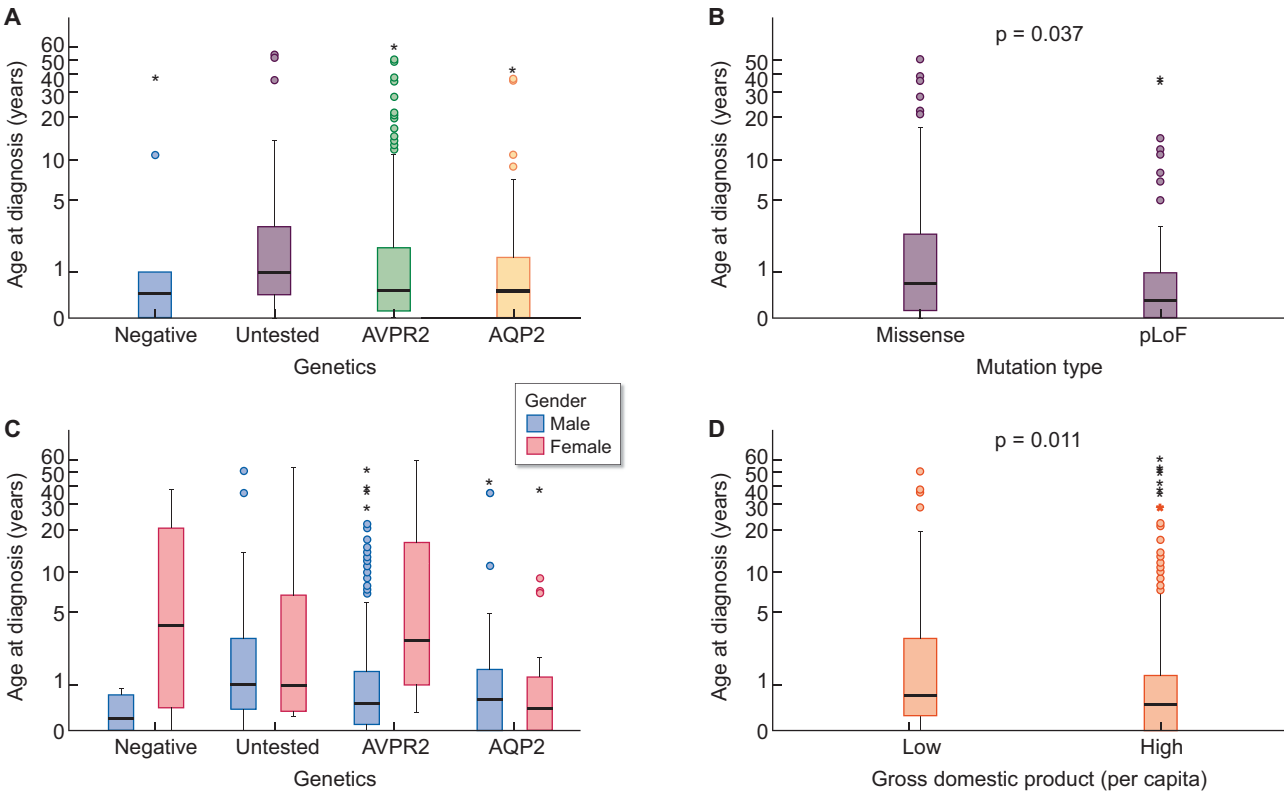

FIGURE 2: Age at diagnosis. Shown is the age at diagnosis in respect to several selected characteristics. (**A**) Genetic group. Note that 90% of patients were diagnosed before the age of 10 years. (**B**) Mutation type. Patients with variants pLoF were diagnosed significantly earlier than those with missense variants. (**C**) Gender and genetic group. Males ($n = 199$, data missing on five individuals) with *AVPR2* pathogenic variants were diagnosed earlier than females ($n = 12$). (**D**) GDP per capita. Patients living in countries with higher GDP ($n = 186$; GDP >15 000$/year) were diagnosed earlier compared with those in lower GDP countries ($n = 121$, GDP <15 000$/year).

Table S4. Distribution of the reported ethnicities showed a high proportion of White/European (81%), followed by Asian (10%) (Figure 1C). A total of 25 genotypes (58 patients) were reported at least twice by the same clinician, suggesting a familial relationship.

The median age (range) was 14.0 (0.1–70) years at last follow-up (Figure 1D) and 110 patients (35%) were adults (≥18 years old).

Age at diagnosis

The majority (58%, $n = 179$) of patients were diagnosed in the first year of life, yet 6% were diagnosed during adulthood (of these, 79% had pathogenic variants). The median age (IQR) at diagnosis was 0.6 (0.1–2.0) years with no significant difference between the genetic groups (Figure 2A). Analysis by variant type (Figure 2B) showed an earlier diagnosis in the group with pLoF compared with missense variants [0.3 (0.0–1.0) versus 0.7 (0.1–2.0) years; $P = 0.037$]. Male patients with pathogenic variants in *AVPR2* were significantly younger at diagnosis than females [0.5 (0.1–1.5) versus 3.1 (1.0–18.3) years; $P = 0.01$; Figure 2C]. Moreover, patients living in countries with higher GDP per capita had an earlier age at diagnosis compared with those in low-income countries [0.5 (0.0–1.4) versus 0.7 (0.3–3.0) years; $P = 0.011$] (Figure 2D).

Auxology

Reported weight and height SDS for both paediatric and adult patients were analysed for the four genetic groups (Supplementary data, Table S5). There was no significant difference for weight SDS between the paediatric groups (Figure 3A). In contrast, there was a significant difference ($P = 0.03$) in adults, showing an increased BMI (mean ± SD) in patients with confirmed variants (29.3 ± 6.2) compared with those with undefined genetic diagnosis (26.0 ± 5.5). Secondary analysis for adult patients from EU28 countries ($n = 68$) showed a significantly elevated proportion of obese individuals in the NDI cohort compared with the reference population (41% versus 16%; $P < 0.001$; Figure 3B). This scenario was reversed for height: paediatric patients with confirmed variants had a significantly ($P < 0.05$) lower height SDS compared with those in the negative group (Figure 3C). This difference was not seen in the adult patients (Figure 3D). Overall, 12.6% of individuals from the entire cohort did have a low height (SDS <−2.0) at last follow-up.

Kidney function

The prevalence of CKD Stage ≥2 in the paediatric age (2–20 years old) was 32%, with most (85%) in Stage 2 (Figure 4A).

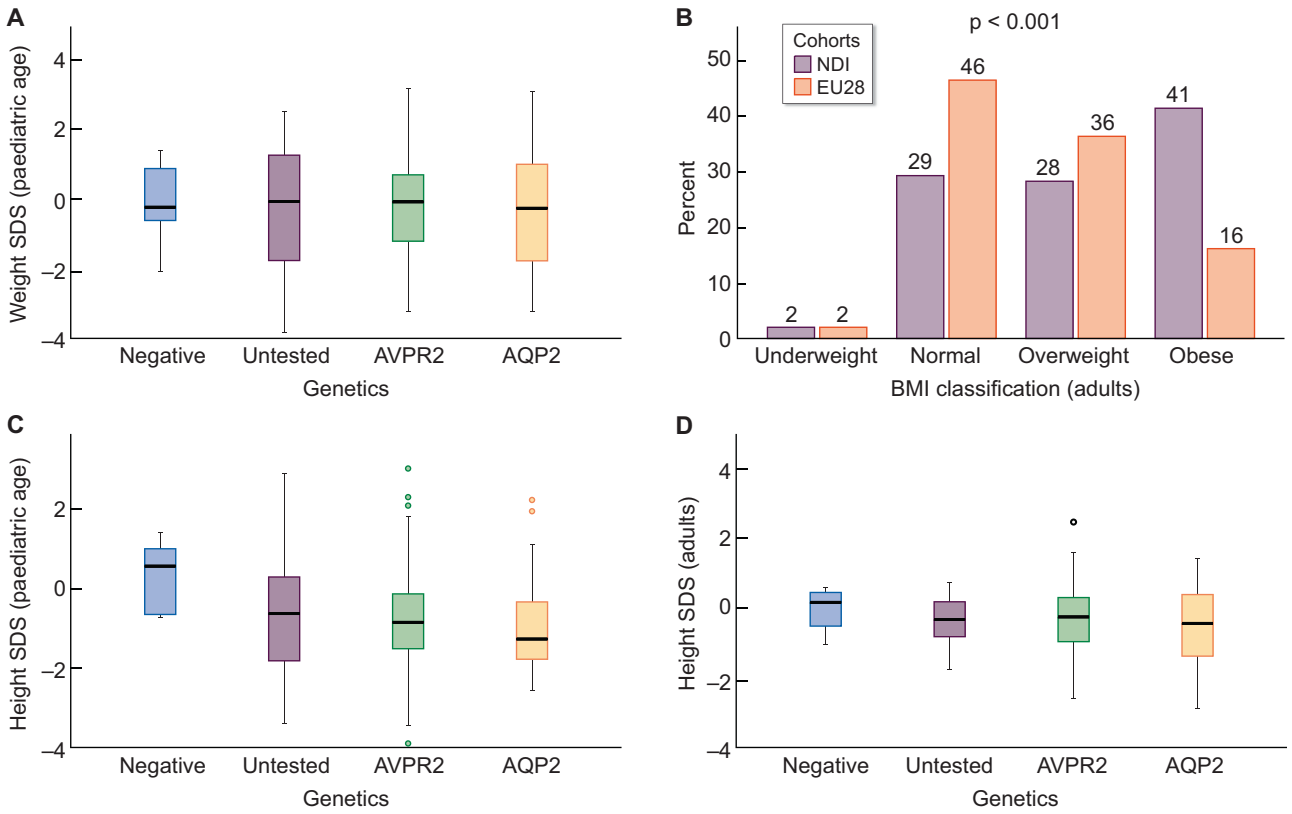

FIGURE 3: Auxology. Shown are data on height, weight and BMI according to selected parameters. (**A**) Boxplot representing weight SDS in paediatric patients according to their genetic group: negative ($n = 7$), untested ($n = 25$), *AVPR2* ($n = 148$) and *AQP2* ($n = 25$). Note the roughly similar distribution across the genetic groups. (**B**) BMI of adult patients (underweight <18.5, normal 18.5–24.9, overweight 25.0–29.9 and obese ≥30.0 kg/m^2). Note the increased prevalence of obese patients in this NDI cohort. (**C**) Height SDS in children according to genetic group. Note that 15% of children had a height <2.0 SDS and that both median (−0.9) and IQR (−1.7 to −0.1) are lower than expected for age. Moreover, height SDS was significantly lower in those with confirmed mutations (*AVPR2*, $n = 147$ and *AQP2*, $n = 24$) compared with those without identified mutation (negative, $n = 7$ and untested, $n = 25$). (**D**) Adult (final) height according to genetic group. Note the essentially normal final height across all genetic groups: negative ($n = 4$), untested ($n = 18$), *AVPR2* ($n = 63$) and *AQP2* ($n = 14$).

Mean (SD) eGFR at last follow-up in adults was 87 (±36) mL/min/1.73 m^2 and was broadly similar across the genetic groups: negative 74 (±35), untested 84 (±44), *AVPR2* 87 (±32) and *AQP2* 97 (±43) mL/min/1.73 m^2 (P = 0.8). Of the 87 adult patients (≥20 years) with eGFR data available, 42 (48%) had CKD Stage ≥2 and one patient with end-stage kidney disease (ESKD) was noted (Figure 4B). The linear estimation of kidney function decline in adults showed a loss of 1.4 mL/min/1.73 m^2/year from 20 years of age with a starting eGFR of 110 mL/min/1.73 m^2 (Figure 4C). CKD Stage ≥2 was significantly (P < 0.001) more common (44%) in NDI patients aged 20–60 years compared with the NHANES III population (26%). The difference was especially pronounced at younger adult age (20–39 years) with a prevalence of 32% ($n = 57$), compared with 14% in NHANES III (Figure 4D). In adult patients, no significant association was found between kidney function and genetic group or GDP. However, in the paediatric group (2–20 years), mean (±SD) eGFR was higher in countries with high income compared with low income [110 (±29) versus 95 (±29) mL/min/1.73 m^2; P = 0.001;

Treatment

From the entire cohort ($n = 315$), 67% were treated (at last follow-up) with thiazide diuretics, 35% with potassium-sparing diuretics and 31% with non-steroidal anti-inflammatory drugs (NSAIDs) (Supplementary data, Table S6). The age distribution for thiazide and NSAID treatments are shown in Figure 5A and B. Prescription of these drugs was significantly (P < 0.001) more prevalent in patients <20 years of age: 44% of adult patients were not prescribed either of these drugs in contrast to 15% of children (Figure 5C). With regards to tube feeding for long-term enteral feeding/hydration, 18% ($n = 59$) had had a nasogastric tube and 7% ($n = 23$) a gastrostomy in place at some point ($n = 247$). The median (IQR) age for tube insertion was <1 month (<1–10) and for removal 2.0 (1.0–3.8) years.

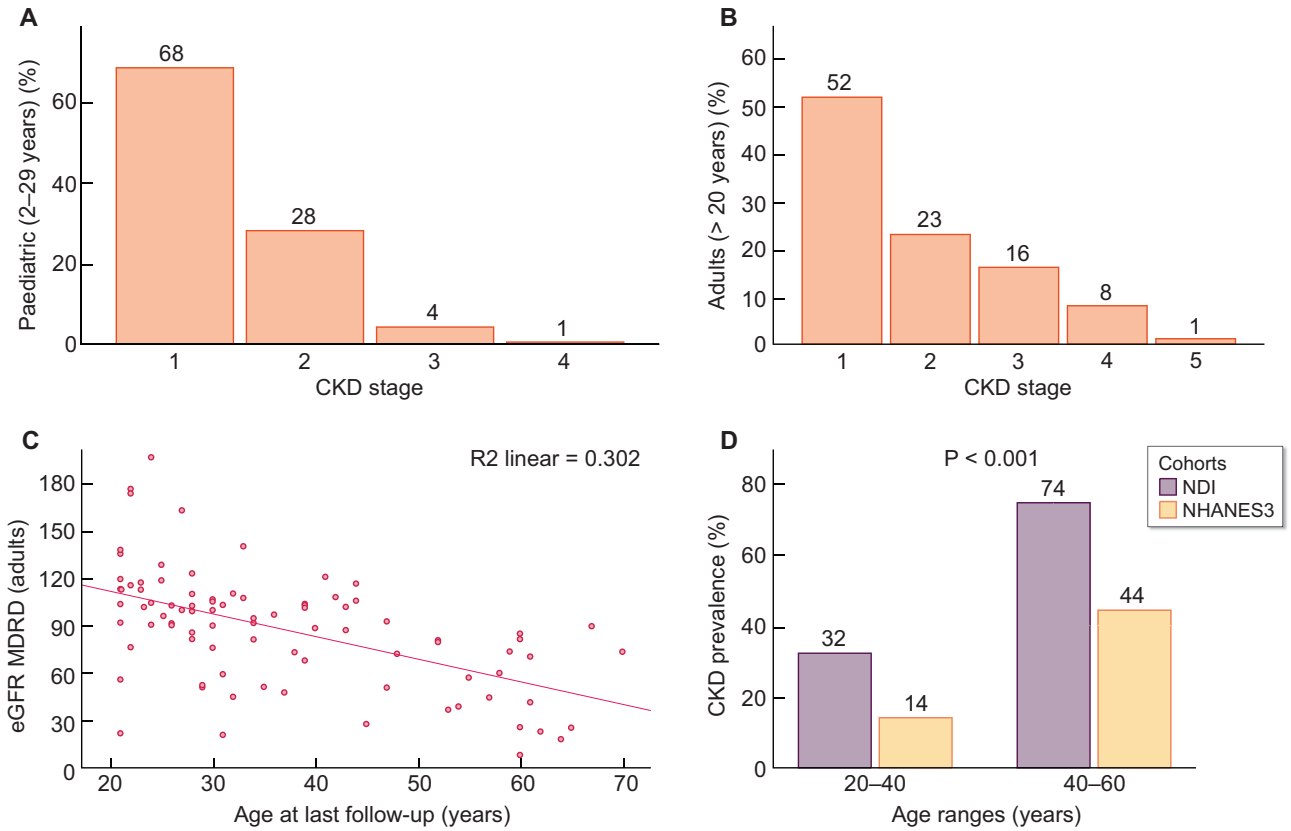

FIGURE 4: Kidney function. Shown are data for eGFR and corresponding CKD changes. (**A**) CKD stage distribution in paediatric (2–20 years, $n = 199$) and (**B**) adult patients ($n = 87$). Note that 5% of children and 25% of adults are in CKD Stage ≥3. (**C**) eGFR in adult patients (>20 years, $n = 87$) against age at last follow-up. Note the kidney function decline estimated at 1.4 mL/min/1.73 m^2 per year with a starting eGFR of 110 mL/min/1.73 m^2 at age 20 years. (**D**) CKD stages in adult patients compared with a reference population (NHANES III). Note the significantly ($P < 0.001$) higher prevalence of CKD in the NDI cohort in both age groups: 20–40 years ($n = 57$) and 40–60 years ($n = 19$).

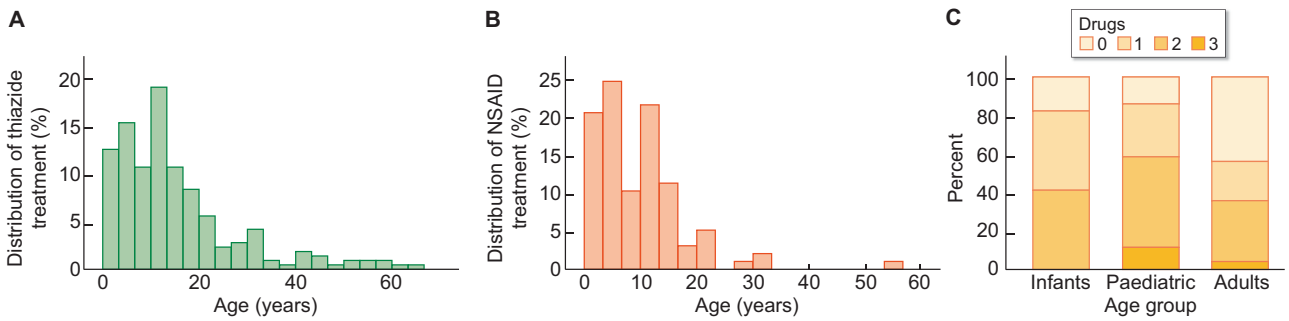

FIGURE 5: Treatment. Shown is the distribution of treatment with specific medications according to age. (**A**) Histograms with distribution of treatment with thiazide diuretics and (**B**) NSAIDs according to age. Note that both treatments are predominantly prescribed during the paediatric age. Patients (73%) receiving a thiazide ($n = 217$) were below the age of 18 years of age, compared with 91% of NSAIDs ($n = 98$) for same age group. (**C**) Number of medications prescribed according to three age groups: infants (<2 years, $n = 17$), paediatrics (2–18 years, $n = 200$) and adults (>18 years, $n = 98$). Note that almost half (44%) of adult patients received no medications, compared with 15% of children, and that the majority of paediatric patients were treated with combination of medications.

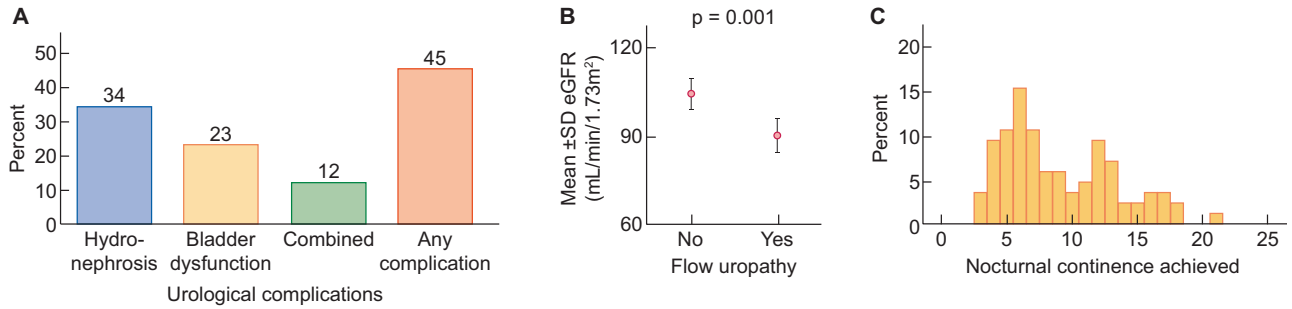

FIGURE 6: Urological complications. Shown is the frequency of selected associated urological complications. (**A**) Frequency of manifestation of flow uropathy (hydronephrosis and/or bladder dysfunction). Note that 45% of patients were reported to have evidence of flow uropathy. (**B**) Flow uropathy and eGFR. Patients with flow uropathy had a lower mean eGFR compared with those without (90 versus 103 mL/min/1.73 m^2). (**C**) Histogram showing the distribution of age (years) at which nocturnal continence was achieved ($n = 85$). Note that the median (IQR) age was 8 (6–12) years, with a wide range of 3–21 years.

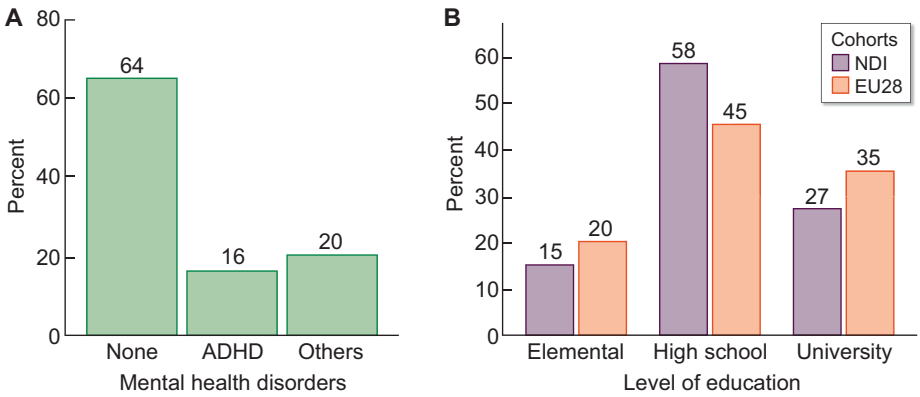

FIGURE 7: Psychosocial aspects. Shown are data on mental health, education and living arrangements. (**A**) Mental health problems reported in the cohort ($n = 178$). Note that more than a third (36%) of patients were reported to have mental health problems, with ADHD being the most frequent single diagnosis. (**B**) Highest completed level of education in patients from EU28 countries aged 25–54 years ($n = 41$) compared with EU28 reference data. Note that NDI patients did not achieve as many academic degrees as expected from the reference population.

Complications

In total, 45% of patients had evidence of flow uropathy. The prevalence of hydronephrosis, bladder dysfunction or both ($n = 266$) was 34, 23 and 12%, respectively (Figure 6A). Of note, eGFR was significantly ($P = 0.001$) lower in those with urological complications compared with those without (90 versus 103 mL/min/1.73 m^2; Figure 6B). Patients of Asian ethnicity had a higher prevalence of flow uropathy (20/27; 74%) than Europeans (83/207; 40%; $P < 0.001$). Other factors such as gender, genetics or medication prescription were not significantly associated with an increased risk of flow uropathy.

Primary nocturnal enuresis was reported in 38% of patients ≥6 years old ($n = 250$) and the median (IQR) age at achieving nocturnal continence was 8 (6–12) years (Figure 6C). There was no significant correlation between enuresis and flow uropathy.

Mental health

Mental health problems were reported in 36% of the entire cohort ($n = 178$), and in 41% of adults, which is significantly ($P < 0.001$) higher than in the general European population (25%) [16]. A diagnosis of ADHD was reported in 16%, which again was significantly ($P < 0.001$) higher than in the general population (5%; Figure 7A). Among demographic variables that correlated positively ($P < 0.05$) with ADHD were: male gender, low GDP and European ethnicity; in contrast, there was no significant correlation with underlying gene, type of variant or medication prescription.

The second most frequent mental health diagnosis was intellectual disability, reported in 9% ($n = 16$). There was no significant association with gender, ethnicity, age at diagnosis and GDP.

Supplementary data, Table S7 details the different mental health disorders identified in our cohort.

Education, employment and living arrangements

For those individuals ($n = 41$) within the 25–54 years age range and belonging to one of the EU28 countries, the highest level of education achieved was primary (15%), secondary (58%) and tertiary (27%) (Figure 7B). When compared with average data from 28 European countries, this NDI cohort has a significantly ($P = 0.03$) smaller proportion of patients achieving an academic degree (EU28: 35%). The rate of patients ≥25 years

of age in full employment was 73%. In the age range of 25–55 years for which comparable general population data are available, there was no significant difference for full-time employment between this NDI cohort (78.4%) and EU28 (80.4%). Patients (79%) in our cohort aged >30 years old were living independently (away from parental home).

DISCUSSION

We report on clinical, genetic and psychosocial data from patients with a diagnosis of primary NDI. To the best of our knowledge, our cohort is the largest reported so far for this condition, spanning an age range of 70 years (Figure 1D) and including patients from 22 countries. More than a third of patients are adults, thereby providing robust data on final height, educational achievement, employment and living arrangements. Our results are thus of relevance to the management and prognosis of patients affected by this rare condition.

Genetics

The vast majority (86%) of patients had genetic testing performed (Figure 1B), with causative variants identified in almost all (96%). This diagnostic yield is roughly similar to previously reported figures, typically around 90–95% [17–19]. As expected, there is a strong predominance of male patients (84%) due to the X-linked inheritance of *AVPR2* variants. However, the proportion of patients with autosomal recessive NDI (16%) is slightly higher than the usually reported 10% [1, 19]. We presume that this reflects a higher proportion of patients from consanguineous background in our cohort, as 69% of *AQP2* variants were homozygous. Of note, the prevalence of *AQP2*-associated NDI in patients from European centres was 12% and thus similar to previous reports.

Age at diagnosis

Most patients were diagnosed in the first year of life (Figure 2A) with the typical presentation of vomiting and growth failure [1]. Nevertheless, 42% of patients were diagnosed later, including 6% diagnosed as adults, the oldest one at the age of 60 years. This reflects the spectrum of severity of this disorder and there are probably several factors leading to such late diagnosis: first, 32% ($n = 6$) of patients diagnosed in adult age were females with confirmed ($n = 3$) or potential (untested or no identified causative variant) *AVPR2* variants, likely reflecting skewed X-inactivation with some AVPR2 expression [20]. Next, some missense variants may not completely abolish functionality of the encoded protein, leading to partial NDI [21–23]. Indeed, patients with pLoF variants were diagnosed at younger age than those with missense variants (Figure 2B). Lastly, this may in part also reflect the healthcare system, as age of diagnosis was later in countries with low compared with high GDP (Figure 2D).

Auxology

Data on growth are overall reassuring: while height SDS was below the average in the paediatric age group, it was still in the normal range (Figure 3C). More importantly, final height in adults is similar to the normal population (Figure 3D), suggesting that the lower height ascertained in childhood may reflect delayed puberty, a common complication of CKD [24]. Of interest is the significantly increased proportion of obesity in adults (Figure 3B), which was most pronounced in those with confirmed variants. Children with NDI typically receive specialist dietetic advice to maximize caloric intake without increasing the osmotic load, so as to provide sufficient calories for normal growth, yet minimizing urine output [1]. This is also reflected in the fact that 25% of children received long-term tube feeding. This treatment appears to work well during childhood as weight SDS in children was similar to the age- and sex-matched general population. However, the increased adult weight potentially reflects ongoing caloric maximization, including perhaps from calorie-containing drinks, even when growth has finished. Our data suggest that ongoing dietetic support into adulthood may be indicated, albeit with the aim of reducing caloric input rather than increasing it. Moreover, as obesity increases the risk for diabetes mellitus, proactive monitoring might be advisable in obese adult patients, especially since one of the cardinal symptoms of diabetes, polyuria, is already present anyway.

Kidney function

Almost a third of patients <20 years of age had CKD Stage ≥2 (5% Stage ≥3) and this increased to 48% (25% Stage ≥3) in the >20-year age group (Figure 4). Using the NHANES III data for comparison in adults, the prevalence of CKD Stage ≥2 is significantly higher in our NDI cohort. While there are no large-scale epidemiological studies of CKD in children, data from registries suggest a prevalence of CKD around 70 per million of the age-related population (<0.01%) [25, 26]. Thus, the prevalence of CKD is significantly higher in NDI patients across all age groups. This may reflect flow uropathy (as those with this complication have lower GFR), kidney injury from repeated episodes of dehydration as well as potential nephrotoxicity of medications, such as NSAIDs. Nevertheless, ESKD is rare and was reported in only one patient.

Drug treatment

Drugs typically used in the treatment of NDI with the aim of reducing urine output include NSAIDs, thiazides and amiloride [1]. A previous single-centre report had suggested that these drugs may be less effective with increasing age and that many patients come off drug treatment during school age [18]. A similar decrease in drug use with age was also reported in a paediatric multicentre study [19]. Our data here appear to confirm this: while >80% of paediatric patients are treated with medications, this decreases to 54% in adult patients (Figure 5).

Urological complications

Nocturnal enuresis is an important problem in paediatric NDI patients, because of the large volumes of urine produced and the attached social stigma [18]. In this study, patients achieved nocturnal continence, albeit delayed at a median age of 8 years.

Flow uropathy and bladder dysfunction, especially bladder enlargement, are recognized complications of NDI, associated with the large urine volumes [18, 27]. Our data suggest that

these complications are present in almost half of all patients, which is similar to another multicentre cohort [19]. Importantly, the presence of this complication was associated with a lower eGFR. Yet, whether this truly reflects kidney damage from the flow uropathy or whether patients with this complication have just more severe disease with potentially more episodes of dehydration cannot be discerned from our data.

Mental health

Very few data on mental health problems in NDI exist. One single-centre study specifically examining this issue reported that almost half of patients fulfilled criteria for a diagnosis of ADHD [2], yet in a separate cohort, a formal diagnosis of ADHD was noted in only 12.5% [18]. Our data here show a prevalence of 16%, more in line with the second study, yet this may be an underestimate as patients may either not have been formally tested or the corresponding nephrologist may not have been aware of the diagnosis. In any case, this prevalence is higher than in the general population (5%) [11]. The fact that the prevalence of ADHD is roughly similar across the genetic groups argues against a gene-specific effect and instead may be related to brain injury from repeated severe dehydration or simply reflects difficulties concentrating because of constant thirst and need to go to the toilet [2].

Perhaps surprisingly, intellectual disability was the second most frequent diagnosis within the mental health disorders, reported in 9% of patients with available data. Early reports of NDI had highlighted complications of severe mental impairment and intracranial calcifications: in one study, 3 of 17 patients had an intelligence quotient $\geq$1 SD below the norm and there are further reports of patients with severe mental impairment [2, 28–30]. This is considered a complication from repeated episodes of severe dehydration that can be avoided with adequate treatment [1]. While the frequency of intellectual impairment in our report is lower than in those earlier reports, it nevertheless remains a problem. Due to the low number ($n = 16$) of patients with reported intellectual disability, statistical analysis to identify potential risk factors did not provide further information. Importantly, the degree of intellectual disability and especially data on formal intelligence assessments were not captured in our study, so that the overall significance of this problem cannot be assessed further.

Education, employment and living arrangements

So far, virtually no data on education and employment have been reported for patients with NDI. While a smaller proportion of patients achieved an academic degree compared with the European average, this likely is not a specific complication of NDI but is in line with the typical decreased educational attainment in children with chronic health conditions, including CKD [31–33]. Encouragingly, the finding that the proportion of 25- to 55-year old patients in full-time employment is similar to the general population and that the vast majority of >30-year-old patients live independently from their parents argues against pervasive intellectual problems.

Limitations

Our study has obvious limitations. Most importantly, this is a retrospective cross-sectional cohort review with data only from the last follow-up, captured via an online form. With any such study, there needs to be a balance between feasibility and the comprehensiveness of the data collected. If large numbers of data are requested, clinicians may be reluctant to participate, as data entry is time-consuming. In the absence of longitudinal data, important questions such as potential causes of CKD, including an association with exposure to NSAIDs, cannot be addressed. This highlights the importance of establishing a comprehensive international registry for a longitudinal data collection. Moreover, no data were provided on maximal urine osmolality after DDAVP, as especially in adult patients transitioned from a paediatric unit, these data may not be readily available. Some patients with partial NDI have reported maximal urine osmolalities exceeding 600 mOsm/kg and this can be clinically difficult to distinguish from central DI [21–23]. It is thus conceivable that a small number of patients in this study may have been misdiagnosed as NDI. However, considering that the vast majority (82%) of included patients had genetic confirmation, this potential diagnostic uncertainty is unlikely to have biased our results, especially since we provide most analysis according to genetic group. The possibility of partial NDI also highlights the wide spectrum of phenotypic severity, which is apparent in most variables analysed. Moreover, databases used for comparison, such as NHANES or EU28, do not necessarily match the composition of our cohort. This needs to be considered when using our data to provide prognostic information to individual patients.

CONCLUSIONS

We provide clinical and social data on a large cohort of patients with NDI. Overall, these suggest a favourable long-term outcome, with patients attaining a normal final height and a similar rate of full-time employment as the general population. While mild CKD is common, ESKD is extremely rare. However, more than half of patients suffer from urological complications and/or mental health problems, respectively. Our data inform the management and prognosis of patients with NDI.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

FUNDING

This work was supported by The European Reference Network for Rare Kidney Diseases. S.C.L.-G. is supported by the William Harvey Research Institute. D.B. is supported by the NIHR Biomedical Research Centre at GOSH/ICH.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Received: 10.5.2020; Editorial decision: 20.7.2020