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# Cognitive and Psychosocial Functioning of Patients With Congenital Nephrogenic Diabetes Insipidus

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Mental retardation (MR) is generally considered one of the main complications of congenital nephrogenic diabetes insipidus (NDI). However, psychometric studies of NDI patients are scarce and outdated. In the present study, 17 male NDI patients underwent psychological evaluation. Total intelligence quotient of 14 patients was within ( $n = 13$ ) or above ( $n = 1$ ) the normal range, 1 patient had an intelligence score between  $-1$  and  $-2$  standard deviations (S.D.) and 2 young patients had a general cognitive index more than 2 S.D. below the norm. Attention deficit hyperactivity disorder criteria were met by 8 out of 17 patients and scores on short-term memory were low in 7 out of 10. No relation between test performances and age at diagnosis or hypernatremia could be found, with the exception of a negative correlation between age at start of therapy and verbal IQ in one age group. Although several explanations for an association between MR and NDI can be postulated, it seems that the current prevalence of MR among patients with this disease is considerably lower than suggested in literature.

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**KEY WORDS:** nephrogenic diabetes insipidus, hypernatremia, cognitive and psychosocial functioning, neuropsychological screening, mental retardation, vasopressin type 2 receptor, cerebral calcifications

## INTRODUCTION

Patients with congenital nephrogenic diabetes insipidus (NDI) lack the ability to concentrate urine in response to the neurohypophyseal hormone arginine vasopressin (AVP). Consequently, as soon as fluid intake is insufficient to compensate for their large renal loss of fluid, disturbance of fluid homeostasis will occur. Especially in the first year of life, patients are at risk of severe, sometimes life-threatening, dehydration. At this age, polyuria and polydipsia are often not manifest. Instead, the clinical picture is dominated by nonspecific symptoms such as vomiting, anorexia, failure to thrive, fever, constipation and developmental delay [reviewed by Knoers and Monnens, 1992]. Accordingly, in most infants diagnosis of NDI is not made until severe hypernatremia occurs.

Mental retardation (MR), varying from mild to severe intellectual impairment, has been reported in patients with NDI and is generally considered to be a sequel of severe brain dehydration [Forssman, 1955; Reuss and Rosenthal, 1963; Bode and Crawford, 1969; Niaudet et al., 1985]. However, the abundance of reports which mention MR as a clinical hallmark of NDI is in striking contrast with the paucity of psychometric data obtained in these patients. Furthermore, the question arises whether the current prevalence of MR among NDI patients has decreased due to improved therapeutic management of the disease.

In the present study, general intelligence, cognitive profiles and psychosocial functioning of 17 male NDI patients were evaluated and related to factors which could predispose these patients to cognitive deficits. In addition, neuropsychological evaluation of visual-motor integration, attention and memory was made to investigate basic functions required for normal learning abilities.

## PATIENTS

Twenty-seven male Dutch NDI patients were known at the University Hospital of Nijmegen, which is the centre where nearly all Dutch NDI patients are referred to for DNA analysis. Twenty-two patients of this group were asked by letter to participate in the study, with a positive response from 17 patients. The 5 patients who did not respond were estimated to be of average intelli-

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gence, since they all attended normal education. Five patients were not approached for different reasons. Two of them were too young to be examined by the tests used in this study and one had, in addition to NDI, diabetes mellitus since childhood. The 2 other patients were severely mentally retarded and therefore not amenable to the tests used in this study. The latter two were evaluated retrospectively.

In the study group ( $n = 17$ ), DNA analysis had shown mutations in the vasopressin type 2 (V2) receptor gene in 14 patients, consisting of 8 missense mutations and 6 nonsense mutations, and compound heterozygosity for two aquaporin 2 (AQP2) missense mutations in 1 patient (Tables I and II). In 2 brothers, DNA analysis was not yet completed, but there was no doubt about the clinical diagnosis and linkage analysis was compatible with X-linked recessive inheritance. Except for patients 2 and 5 (brothers), 6 and 9 (brothers) and 3 and 14 (nephew/uncle), patients were unrelated. In 2 of the 14 families, additional patients ( $n = 5$ ) had been identified, of whom only one had been treated for a short time. Four of these patients (aged 23–52 years), all relatives of patient 8, were working at a protected employment setting, where simple work is carried out under close supervision. They were not willing to participate in our study. The fifth patient (aged 53), the uncle of patient 12, was known to be mentally retarded and to be living in a protected environment, but additional information was not available. Family history did not show other mentally retarded individuals. None of the patients in the study group had a history of prematurity or perinatal asphyxia. All socioeconomic segments appeared to be represented. Except for patients 6 and 8, all patients were right-handed.

The 2 oldest patients of our NDI population, 2 brothers (aged 39 and 37, respectively) in whom a missense V2 receptor gene mutation (S167L) had been detected, are both severely retarded and were therefore not able to participate in our study protocol. Fragile X syndrome had been excluded in both. They were macrocephalic (skull circumference  $> P 90$ ) but had no specific dysmorphic features. Parents and the nonaffected brother and sister are of normal intelligence. In the eldest brother, respiration directly postpartum was reported to be insufficient. Diagnosis of NDI was not made until

the age of 2½ years. Therapy initially consisted of salt restriction and ample fluid supply, followed by start of chlorothiazide and potassium one year later. Routine measurements of serum sodium were repeatedly reported to be around 160 meq/l. At the age of 4.5, severe electrolyte imbalance occurred with a maximum sodium level of 225 meq/l. Motor development was delayed: he did not stand until 2½ years of age and started walking at the age of 5. At the age of 4½, he was institutionalized. Psychological testing has demonstrated severe MR (IQ  $< 30$ ). Skull X-rays made at the age of 33 revealed no calcifications. In the younger brother, no signs of perinatal asphyxia had been noticed. At the age of 8 months, he was recognized to have NDI. Medication was initiated soon thereafter, but, similar to his brother, adequate therapeutic management of the disease appeared to be difficult and he was admitted for hypernatremia several times (sodium values unknown). He showed a less retarded motor development than his brother, with standing at the age of 2 and walking at the age of 2.5. When he was 10 years old, he was institutionalized. He functions at high imbecile level (IQ 46) and shows autistic behavior.

## MATERIALS AND METHODS

### Cognitive Assessment

Cognitive functioning of the youngest children, aged 3 to 6 ( $n = 5$ ), was assessed by the Dutch adaptation of the McCarthy Developmental Scales of Children's Abilities [McCarthy, 1972]. The 18 subtests are ordered into four cognitive subscales, consisting of a verbal, a perceptual performance, a quantitative, a memory scale and one motoric subscale which was not included in this study. The verbal, performance and quantitative subscales indicate the general cognitive index (GCI, mean = 100, S.D. = 16). All subscale scores are T scores (mean = 50, S.D. = 10).

Intellectual abilities of the patients aged 7–16 ( $n = 8$ ) and patients aged 17–30 ( $n = 4$ ) were measured by the Dutch adaptation of the Wechsler Intelligence Scale for Children-Revised (WISC-R) [Wechsler, 1974] and the Wechsler Adult Intelligence Scale (WAIS) [Wechsler, 1971], respectively. The total intelligence quotients (IQ) of the WISC-R and WAIS are based on a series of subtests. These subtests are ordered in two groups which

TABLE I. Medical and Psychological Data for Patients Aged 3–6 Years

No.	Gene	Age at diagnosis	Max. Na <sup>+</sup> (mmol/l)	Months in hospital in first 2 yr	School	Age at evaluation	GCI <sup>a</sup>	Ve <sup>b</sup>	Pe	Qu	Me	ADHD <sup>c</sup>	CBCL <sup>d</sup>
1	V2R <sup>e</sup>	1y	165	0.75	nursery school	3y 3m	105	53	60	42	43	–	53
2 <sup>f</sup>	V2R	1y 9m	156	1.00	specialized nursery	36 3m	90	49	44	36	45	–	38
3	V2R	9m	174	0.75	nursery school	3y 10m	58	28	37	26	<22	+	42
4	V2R	1y 3m	149	0.50	nursery school	5y 4m	100	57	53	48	53	–	53
5 <sup>f</sup>	V2R	4y 5m	155	0.50	specialized nursery <sup>g</sup>	5y 11m	64	33	28	32	31	+	42

<sup>a</sup>GCI, general cognitive index.

<sup>b</sup>Ve (verbal), Pe (perceptual), Qu (quantitative), and Me (memory) subscales according to McCarthy in T-scores (mean 50, S.D. 10).

<sup>c</sup>ADHD, attention deficit hyperactivity disorder.

<sup>d</sup>CBCL, Child Behaviour Checklist (mean 50, S.D. 10).

<sup>e</sup>V2R, V2 receptor gene.

<sup>f</sup>Siblings.

<sup>g</sup>Change to specialized school for mentally retarded children after examination.

TABLE II. Medical and Psychological Data for Patients Aged 7–16 Years (WISC-R) and 17–30 Years (WAIS)

No.	Gene	Age at diagnosis (start therapy)	Max. Na <sup>+</sup> (mmol/l)	Months in hospital in first 2 yr	School <sup>f</sup>	Age at evaluation	TIQ <sup>a</sup>	VIQ <sup>b</sup>	PIQ <sup>c</sup>	ADHD <sup>d</sup>	CBCL <sup>e</sup>
WISC-R											
6 <sup>h</sup>	–	0.5m (3.5)	163	0.50	elementary	7y 2m	101	101	101	–	55
7	V2R <sup>g</sup>	1y 4m	158	1.75	elementary <sup>i</sup>	7y 3m	81	88	77	+	27
8	V2R	9m (25)	155	0.75	elementary	9y 8m	89	75	108	+	34
9 <sup>h</sup>	–	3.5m	159	2.00	elementary	10y 3m	103	104	101	–	42
10	AQP2 <sup>j</sup>	2.5m (3)	170	6.25	elementary	11y 4m	89	93	87	+	39
11	V2R	2.5m	183	3.00	secondary (intermediate level)	13y 7m	94	99	90	+	65
12	V2R	2.5m	166	15.00	secondary (intermediate level)	13y 10m	99	101	97	+	49
13	V2R	3m	166	12.00	secondary (lower level)	15y 6m	90	93	88	+	39
WAIS											
14	V2R	2.5m	170	6.75	secondary (intermediate level)	17y 11m	118	116	118	–	–
15	V2R	8.5m	176	5.75	special school for learning disabilities	19y 2m	88	83	96	–	58
16	V2R	10y 8m	151	5.50	secondary (lower level)	19y 2m	98	99	98	–	–
17	V2R	6.8m	153	11.00	secondary (intermediate level)	30y	109	116	98	–	–

<sup>a</sup>TIQ, total intelligence quotient.

<sup>b</sup>VIQ, verbal IQ.

<sup>c</sup>PIQ, performal IQ.

<sup>d</sup>ADHD, attention deficit hyperactivity disorder.

<sup>e</sup>CBCL, Child Behaviour Checklist (mean 50, S.D. 10).

<sup>f</sup>Current or completed form of education.

<sup>g</sup>V2R, V2 receptor gene.

<sup>h</sup>Siblings.

<sup>i</sup>Change to specialized school for mild learning and behavior disabilities after examination.

Age at start of therapy is shown between parentheses when not the same as age at diagnosis.

<sup>j</sup>AQP2, aquaporin 2 gene.



measure verbal IQ and performance IQ, respectively. Mean value of the total, verbal and performance IQ is 100 (S.D. = 15). In order to facilitate comparison among WISC-R and WAIS subtests, the standard scores of the WISC-R were converted to T scores. Verbal and spatial abilities, concentration and distractibility were evaluated by reorganization of the WISC subtests [Banatyne, 1974; Kaufman, 1975].

### Neuropsychological Screening

All patients were given the Developmental Test of Visual-Motor Integration (VMI) [Beery, 1989] to evaluate the age-related development and integration of perceptual and motor skills. To examine aspects of attention and memory, an additional series of neuropsychological tests was given, which only applies to persons above the age of 9 ( $n = 10$ ). The Dutch translation of the Stroop Color-Word Test was used to investigate the capacity to sustain attention independent of intruding or interfering stimuli [Comalli et al., 1962]. The adult form of Reitan's Trailmaking Test (TMT) [Reitan and Wolfson, 1985], which has been standardized for the whole age range, was applied to measure attention and sequential visual processing (Part A) and ability to shift attention (Part B) [Lezak, 1983]. Verbal memory was screened by the Dutch translation of the Auditory-Verbal Learning Test (AVLT) [Rey, 1964]. Retention was measured after 15 minutes. The Benton Visual Retention Test (BVRT) [Benton, 1974] was used to assess visual short-time memory by drawing geometric figures immediately after an exposure of 10 seconds. The WISC-R subscale Mazes was added because of its sensitivity to complex mental functioning involving determination and organization of steps in goal-directed behaviour. The WAIS does not include this test, but it is allowed to use the Mazes and its highest WISC-R norm (16.0–16.5) to estimate the adequacy of the adult performance [Lezak, 1983].

### Psychosocial Functioning and School Achievement

Patients aged 7 to 30 ( $n = 12$ ) were administered the Dutch Personal Inventory adapted to patients with somatic diseases [Luteijn et al., 1989], a self-report which gives insight into personality traits like emotional stability, social competence and self-esteem. Daily activities, social competence and school achievement were evaluated by the three competence scales of the Child Behaviour Checklist (CBCL, mean 5 50, S.D. 5 10) [Achenbach and Edelbrock, 1983], adapted for the Dutch population. Parents of children aged 5 to 16 answered this questionnaire and were subsequently asked to exemplify some of the answers.

During the test sessions, standard observations according to Sattler [1988] were made in order to evaluate emotional status and behavioral patterns suggestive for brain damage. In addition, the criteria of the Diagnostic and Statistical Manual of Mental Disorders (3rd revised edition, American Psychiatric Association, 1987) for Attention Deficit Hyperactivity Disorder (ADHD) were applied.

### Clinical Data

The following clinical data were obtained from medical records of the patients: age at diagnosis, age at start of therapy, highest registered serum sodium level and months spent in hospital during the first two years of life for reasons related to dehydration.

### Statistical Analyses

Means and standard deviations were computed for all measures of the McCarthy scales, WISC-R and WAIS. Two-tailed T-tests were used to compare the means of the different subtests and subscales and one-tailed paired T-test to assess directional differences. To investigate linear relationships between medical and psychological data, Pearson-R coefficients of correlation were computed for those variables which were measured on interval scale. Statistical evidence was found at a  $P$ -level of  $<.05$ . To reduce the probability of type I errors in the paired T-tests,  $\alpha$  was divided by the number of T-tests according to the Bonferroni procedure, resulting in an  $\alpha$  of 0.004 (0.05/12) for data of the group aged 7–30 and an  $\alpha$  of 0.01 (0.05/5) for data of the youngest age group. All data were analyzed by an SPSS/PC<sup>+</sup> program.

Test administrations, parental interviews and observations were carried out by the same examiner in all patients.

## RESULTS

### Cognitive Assessment

Clinical data, GCI, ADHD diagnoses and McCarthy subscales of the 5 children aged 3 to 6 are shown in Table I. According to the GCI scores, patients 3 and 5 were mentally retarded. Patient 3 had the highest recorded serum sodium concentration of this age group and was the only patient who developed seizures during rehydration. In patient 5, the finding that his younger brother (patient 2), who was diagnosed nearly 3 years earlier, had a GCI within the normal range, suggests a negative influence of the large diagnostic delay. The remaining two patients (1 and 4) showed an average cognitive development. Mean GCI score of this group of five children was  $84.6 \pm 20.2$ . Means of the quantitative and memory subscales were more than 1 S.D. below the means of the normal population.

Table II presents the clinical data and results of psychological evaluation of the patients aged 7 to 16 (WISC-R group,  $n = 8$ ) and 17 to 30 (WAIS group,  $n = 4$ ). Mean total IQ of the total group ( $n = 12$ ) was  $96.6 \pm 10.3$ . The one patient (patient 7) with a total IQ more than 1 S.D. below the mean of the normal population, had been diagnosed relatively late. All other patients, including the patient with the largest diagnostic delay of the whole group, scored within ( $n = 10$ ) or above ( $n = 1$ ) the normal range. Mean total IQ of the WISC-R group was  $93.25 \pm 7.42$  and of the WAIS group  $103 \pm 11.3$ . In the WISC group, a significant negative correlation was found between age at start of therapy and verbal IQ ( $r = -.90, P < .01$ ).

Except for the relationship mentioned above, neither in the total group, nor in the 3 subgroups, could a sig-



nificant correlation be found between age at diagnosis or start of therapy, highest recorded sodium level or time spent in the hospital related to dehydration during the first 2 years of life on the one hand and the results of psychological assessment on the other. Patients with low to moderate intelligence scores did not share a specific site or type of mutation. In fact, the highest and lowest scores were obtained in 2 patients (3 and 14 from one family).

The WISC-R and the WAIS group showed a mutually similar cognitive profile (Fig. 1), but the WAIS group scored higher at nearly all subtests. In both groups, scores on comprehension were significantly higher than scores on arithmetic ( $P < .004$ ).

### Neuropsychological Screening

Mean T scores on VMI for the 3 age groups were  $44 \pm 7.4$  ( $n = 5$ ),  $46.63 \pm 7.35$  ( $n = 8$ ) and  $41.75 \pm 6.44$  ( $n = 4$ ), respectively. Five patients scored 1 S.D. or more below the mean of the normal population (patients 7, 8, 13, 15 and 16). Most errors were made in the three-dimensional figures. Additional neuropsychological testing of the 10 oldest patients showed that 3 patients had scores of 1 S.D. below the mean of the normal population on the Stroop Color-Word test (patients 8, 12, and 15). On the TMT, 3 patients (9, 13, and 17) showed low performances on Part A, but scored in the normal range on Part B, indicating that they had problems with visual tracking but not with the ability to shift. Two patients (15 and 16) scored more than 3 S.D. below the mean of the normal population on both Part A and Part B. In 7 of the 10 patients, verbal short-term memory, as measured by the learning trial of the AVLT, was equal to or more than 1 S.D. below the mean. In all patients, performance on the retention trial was in the

normal range and equal to or better than on the learning trial. At the BVRT, deviation scores of 7 patients were 1 to 6 errors below the norms for age and IQ. Errors were mostly made in the small peripheral figures of the three-figure design and consisted of perseverations, misplacements and distortions. During the exposure time, most patients verbalized the parts to facilitate remembering. The 7 patients who scored low on the AVLT had low scores on the BVRT as well. In the WISC group, mean T score of the WISC subtest Mazes was average ( $50.5 \pm 6.82$ ) whereas in the WAIS group, it was nearly 1 S.D. below the mean ( $41.75 \pm 6.5$ ).

### Psychosocial Functioning

Play observation in the youngest children ( $n = 7$ ) demonstrated that only 3 children played in an age-related way (patient 1, 4 and 6). The other children were not interested in the play material or built something in a distorted way and left the table within a few minutes. ADHD criteria were met by 8 children. Five out of 10 patients tested with the Dutch Personal Inventory showed a pronounced lack of self-esteem, especially in social situations. Mean T score ( $n = 14$ ) on the competence scale of the CBCL was  $45.36 \pm 10.42$ . Eight of the 14 children scored low or very low on the activity scale, with only one patient being member of a sporting club. Parents associated this general lack of activity with the tiredness which the children complained of frequently. Four children scored below  $-1$  S.D. on the social scale. Three children were members of a youth association and 2 had other outdoor hobbies. Nearly all parents, except those of the two youngest, reported that their children had good contact with a few friends but preferred to play alone. They all mentioned that polyuria and polydipsia seemed to hamper social interactions. In this regard, the clinical presentation of patient 16 is illustrative. Although polyuria and polydipsia had been present since childhood, these signs had been overshadowed by severe behavioral problems, resulting in the psychiatric diagnosis of borderline personality disorder. It was not until, at the age of 10, his behavior necessitated institutionalization, that his polyuria and polydipsia received appropriate medical attention, shortly thereafter resulting in diagnosis of NDI. After withdrawal of the fluid restrictions imposed on him in the past and start of medication, his behavior improved.

### School Achievement

Of the 9 children who visited elementary or secondary schools, the CBCL showed subnormal scores on general school performance in 6 (4 patients between  $-1$  and  $-2$  S.D., 2 patients below  $-2$  S.D.) and insufficient results on arithmetic in 7. After examination, 2 children changed to specialized schools (Tables I and II). Five parents reported restlessness in school and difficulty in concentrating on homework.

### Clinical Data (See Tables I and II)

None of the patients of the study group had demonstrated signs of asphyxia at birth. In the majority of patients (82%), diagnosis of NDI had been made within

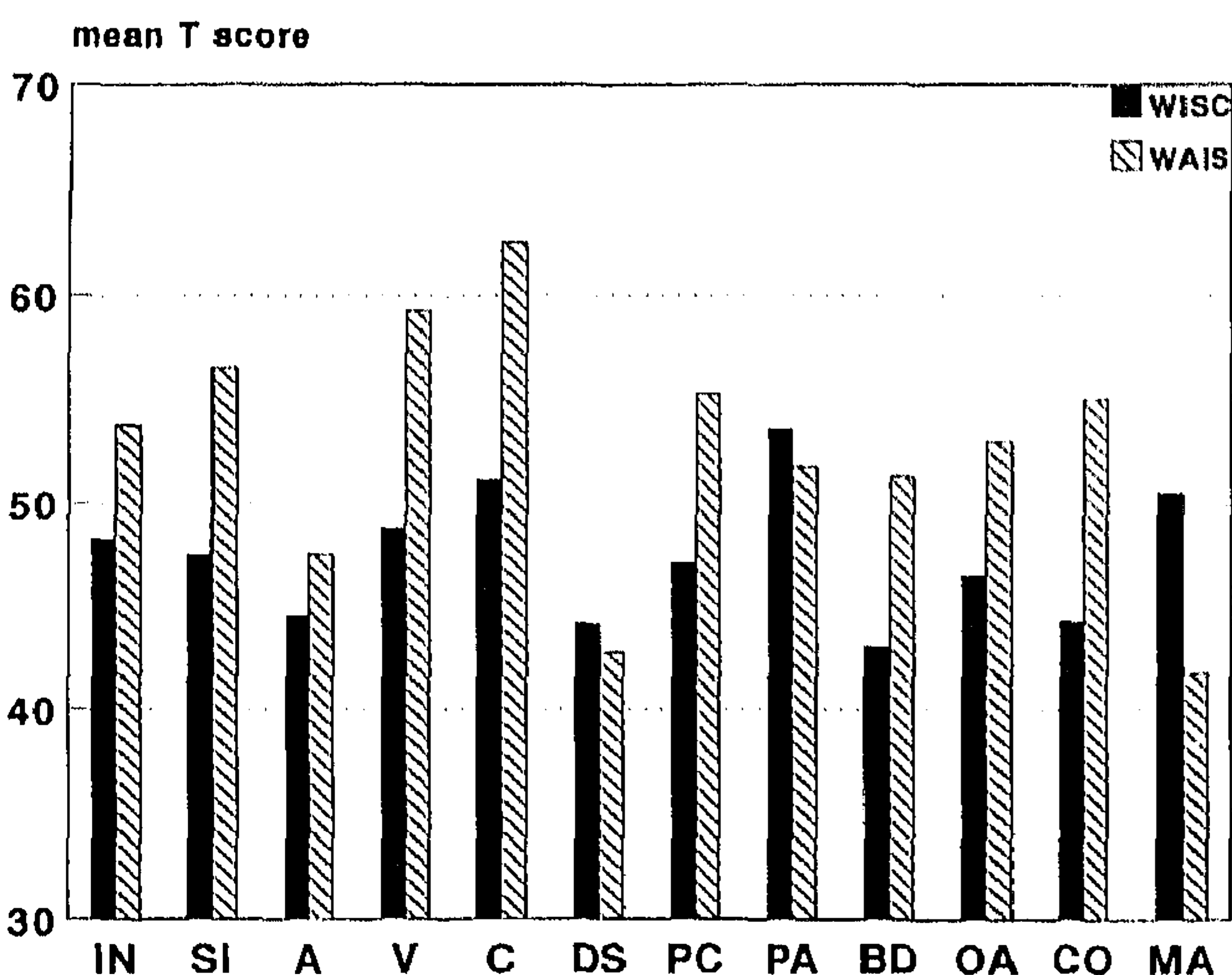


Fig. 1. Mean T scores on subscale measures of the Wechsler Intelligence Scales (mean 50, S.D. 10) of the WISC-R group ( $n = 8$ ) and the WAIS group ( $n = 4$ ). IN, Information; SI, Similarities<sup>1</sup>; A, Arithmetic<sup>2</sup>; V, Vocabulary<sup>1</sup>; C, Comprehension<sup>1</sup>; DS, Digit Span<sup>3</sup>; PC, Picture Completion<sup>2</sup>; PA, Picture Arrangement; BD, Block Design<sup>2</sup>; OA, Object Assembly<sup>2</sup>; CO, Coding<sup>3</sup>; MA, Mazes (<sup>1</sup> verbal abilities and <sup>2</sup> spatial abilities according to Bannatyne [1974]; <sup>3</sup> distractibility factor according to Kaufman [1975]).



the first 18 months of life. In all patients except one, medication (hydrochlorothiazide/indomethacin) had been initiated directly after or within 3 months after diagnosis. Only in patient 8 had medication been started 16 months later. During the past 6 years, in most patients, indomethacin has been changed for amiloride, which is equally effective but has fewer side effects. Nearly all admissions related to dehydration took place in the first two years of life.

### DISCUSSION

Ever since the first description of NDI by McIlraith in 1892, MR has been associated with this disease and generally been attributed to its main characteristic, i.e., dehydration. Dehydration can cause permanent brain dysfunction, manifested by an increased prevalence of MR and convulsive disorders, and autopsy reports have demonstrated several cerebral abnormalities including extensive intracranial hemorrhage, thrombosis and diffuse encephalopathy with focal necrosis and small hemorrhages [Finberg, 1959; Macaulay and Watson, 1967]. Events of this nature might occur in patients with NDI. Additional evidence underscoring the assumption that NDI has adverse effects on the cerebrum is provided by several reports describing intracranial calcifications in NDI patients, lesions which are generally considered a sequel of hemorrhage or necrosis (references in Table III). Besides constituting a possible cause for these macroscopic abnormalities, brain dehydration is also known to have profound effects at the cellular level [reviewed by Strange, 1992]. Plasma hypertonicity has been found to disrupt the blood-brain barrier by opening tight junctions between endothelial cells. Moreover, in an attempt to regain and maintain cellular volume, several processes occur, including the accumulation of organic solutes like inositol, taurine and glutamine. Although meant to be protective, the presence of these osmolytes is thought to have adverse consequences as well, especially during rapid rehydration.

In addition to osmotic imbalance, the genetic defect of patients with NDI has been suggested to be a factor involved in the pathogenesis of MR [Brownstein and Lolait, 1993]. In most patients, NDI is caused by mutations in the X-chromosomal V2 receptor gene [Rosenthal et al., 1992; reviewed by Knoers and Monnens, 1992]. These patients not only lack the anti-diuretic V2 receptor-mediated effect but also the hemodynamic, coagulation and fibrinolytic responses to the V2 receptor agonist 1-desamino-8-D-arginine vasopressin (DDAVP), indicating a generalized V2 receptor defect [Kobrinisky et al., 1985]. Studies in rats have shown that, at least at a certain stage of development, expression of the V2 receptor gene occurs in the brain [reviewed by de Wied et al., 1993; Hirasawa et al., 1994]. Therefore, it can be argued that inability to accomplish V2 receptor-mediated cerebral processes has repercussions on mental functioning of patients with X-linked NDI.

Despite this variety of factors that could contribute to an increased prevalence of MR or cerebral lesions among patients with NDI, caution for bias is warranted. Mentally retarded NDI patients are more likely to be examined for cerebral abnormalities and to be reported in literature. Moreover, the lack of recent psychometric studies might result in an outdated, unduly negative, prognosis of mental development. In the present study, the prevalence of MR among patients with NDI was assessed by studying cognitive functioning of a major part of our NDI population. The results suggest that prevalence of MR in patients with NDI is lower than suggested in literature [Forsmann, 1955; Ruess and Rosenthal, 1963; Bode and Crawford, 1969]. In our study group of 17 patients, 2 young patients were mentally retarded, 1 patient had a total IQ between  $-1$  and  $-2$  S.D., 13 patients scored within the normal range and 1 had a high intelligence level. In order to avoid distortion of facts, we also described the 2 severely retarded patients of our NDI population. Only in the elder brother could several explanations for his degree of

TABLE III. Patients With NDI and Cerebral Calcifications Reported in Literature

Reference	Age at diagnosis	Age at evaluation	Location of cerebral calcifications			Cognitive development
			Basal ganglia	Frontal	Other	
Kanzaki et al. [1985]	2y 11m	2y 11m	-	+	temporal, occipital	17m delayed
Freycon et al. [1988]	11y	18y, 25y	+	+		IQ 60
Schofer et al. [1990a] <sup>d</sup>	9y	16y, 23y	+	+		IQ 60
	6m	4y	+ <sup>e</sup>	+		IQ 40-45
	4 weeks	6y	+	+		2y delayed, improving
Schofer et al. [1990b]	7m	7m, 14m	+	+	parietal, occipital	n.m. <sup>f</sup>
	10y	17y, 19y	+	+	disseminated	severe MR <sup>g</sup>
	14y	14y, 25y	+	+	disseminated	severe MR
Di Rocco et al. [1991]	n.m.	15y	+	+	parietal lobes	n.m.
Nozue et al. [1993]	6y	6y	+	+	temporal, parietal, occipital	normal
Mendonca et al. [1993]	3.5y	18y	-	+		severe MR
Tohyama et al. [1993]	2y 10m	19y	+	+	occipital, parietal	IQ <40
	8m	17y	+	-	occipital	IQ 79

+ , present; - , absent.

<sup>f</sup>n.m., not mentioned.

<sup>g</sup>MR, mental retardation.

<sup>d</sup>At autopsy.

<sup>e</sup>All patients except one (Schofer 1990a) are male.

mental disability be found, namely extreme hypernatremia, a relatively late diagnosis and perinatal problems. In the younger brother, we were not able to demonstrate a predisposing factor. However, four decades ago, management of NDI could have been less optimal, providing an explanation for the high incidence of mental retardation in the older literature as well. The favorable outcome in most of our patients might also be explained by the generally young age at diagnosis in our study group, even in the oldest age group. In fact, results of the youngest age group, which included the two most severely retarded children, were the lowest. Although this age group is too small to allow firm conclusions, it is possible that development is maximally delayed in the first years of life, with a catch-up occurring later in childhood. This tendency can also be discerned in the study of Reuss and Rosenthal [1963] and has been alluded to by Niaudet et al. [1985] as well, but needs to be confirmed by longitudinal studies. Notwithstanding the generally accepted benefit of an early diagnosis, no significant relation could be detected between age at diagnosis and intelligence. Age at start of therapy correlated with verbal IQ in a subgroup of patients only. It can be postulated that when a patient has obtained enough independency to fulfill his high fluid demands, the influence of such factors decreases, leaving a short period during which these can induce variability in outcome, especially when assessing a relatively small group of patients. Moreover, other factors like intercurrent illnesses and environmental factors might confound the relationship between hypernatremia and outcome. With respect to the relation between hypernatremia and intelligence, similar remarks can be made. In addition, the highest recorded sodium level might be a less reliable parameter due to its dependency on frequency of monitoring. In other studies, it was also found to be of little prognostic value [Macaulay and Watson, 1967]. A measure like time spent in the hospital for reasons related to dehydration, did not correlate with intelligence either.

Although, in general, intelligence of our patients was not severely impaired, remarkable findings were the generally low scores on subtests measuring concentration and distractibility and a high prevalence of ADHD. These deficits have been attributed to dysfunction of the frontal lobe [Lezak, 1983; Shue and Douglas, 1992], a region which, in NDI patients, is frequently affected with calcifications (Table III). Attention deficits could also be involved in the low short-term memory scores [Douglas, 1984]. Moreover, although the exact mechanism has not been unravelled yet, AVP as well as its V2 receptor specific agonist DDAVP, have been found to influence learning and memory processes [Beckwith et al., 1990; de Wied et al., 1993]. In this respect, the hypothesis that a cerebral V2 receptor is normally involved in these functions is intriguing. Nevertheless, it cannot be excluded that another receptor is involved [de Wied et al., 1993] or that the effects of DDAVP on mental processes occur indirectly, for instance, by influencing water homeostasis or suppressing intracerebral AVP production [Robinson et al., 1990]. An interesting approach to investigate this hypothesis would be to study the prevalence of mental deficits in NDI pa-

tients with an AQP2 gene defect. Since these patients have normal V2 receptors, the hypothesis of involvement of a V2 receptor in cerebral processes would be confirmed by a lower prevalence of MR or specific cognitive deficits among these patients. Unfortunately, the number of identified AQP2 patients is still small. The test results of the one patient included in this study did not clearly differ from those of the other patients.

Likewise, comparison of the occurrence of cerebral calcifications in V2R-NDI, AQP2-NDI and central diabetes insipidus could provide new insights into the cause and consequences of these lesions. In a large study of patients with central diabetes insipidus in which CT scans were performed, no cerebral calcifications were mentioned [Greger et al., 1986], suggesting that they are specific for the nephrogenic form. However, they do occur in a large variety of other diseases [Kendall and Cavanagh, 1986] and have been reported in a child with a normal renal response to AVP, who developed hypernatremia as a result of hypodipsia [Hammond et al., 1986]. Presence of calcifications in the basal ganglia, a frequently affected region in NDI (Table III), is especially regarded as a nonspecific finding [Puvanendran et al., 1982; Kendall and Cavanagh, 1986]. It seems that these highly vascularized, neuron-rich structures are very vulnerable to a variety of factors, including hypernatremia. Whether the presence of intracranial calcifications relates to MR is not completely clear. Notwithstanding the possibility of selection bias, a high association can be inferred from Table I. Of the 13 NDI patients with cerebral calcifications reported in the literature, at least 8 were mentally retarded, whereas in only 1 case a normal intelligence was mentioned. Furthermore, Tohyama et al. [1993] and Mendonca et al. [1994] both described an early diagnosed patient who was not retarded and had no calcifications in contrast to their elder brothers. In our patient group, only a CT scan of the patient with the highest total IQ was available, which showed slight calcification of the basal ganglia.

In conclusion, the majority (82%) of a group of NDI patients aged 3 to 30 years had an intelligence within the normal range. This finding indicates that, possibly as a result of improved management of the disease, MR can no longer be regarded a clinical hallmark of NDI.

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