Advances in medical care, including improvements in dialysis and transplantation, have increased the survival rates for children with end-stage renal disease (ESRD). However, it is clear that this chronic disease has adverse effects on growth and development, and results in increased risk for developmental delay,1,2 neurological abnormalities,1 and neuropsychological deficits.4,5 Age of onset of ESRD is associated with outcome.6 Children with congenital ESRD had poorer fine motor coordination and more difficulty on tests of verbal and non-verbal long term memory than children with acquired ESRD.7 These groups were comparable on many other measures including intelligence and academic achievement. Transplantation can improve developmental, psychosocial, and neuropsychological outcome,8–11 although persistent neuropsychological deficits have been reported following successful renal transplantation.12 A recent adult outcome study indicated that adults with ESRD since childhood had lower educational and academic achievement.12

Even with improvements in medical management of children with ESRD, there are continuing concerns about their outcome. In this paper we describe the neuropsychological functioning of children with ESRD who had not yet been transplanted compared to sibling controls.

**METHODS**

**Patient selection**

Children 6–16 years of age in end-stage renal failure at the time of evaluation had a glomerular filtration rate of less than 0.3 ml/second/1.73 m² surface area (SI units). They were patients at two academic teaching children’s hospitals in Vancouver and Halifax, Canada. All patients were on a renal transplant waiting list and either pending dialysis or on dialysis therapy. Children with ESRD syndromes which were known to influence neuropsychological functioning were excluded. Physically healthy siblings closest in age to the probands were selected as controls for social and environmental backgrounds. Twenty five patient-sibling pairs were identified for the study but two pairs were not assessed because of scheduling problems, and one family declined to participate. Twenty two patient-sibling pairs were evaluated. Using Hollingshead’s criteria for socioeconomic status,13 the sample was predominantly middle class. There was an equal number of males and females in both the ESRD and sibling control groups. The mean age was 141.8 months (SD 39.2) for the ESRD group and 140.7 months (SD 37.1) for their sibling controls, indicating that their ages were comparable. The sample was representative of children with non-syndromic ESRD because there are no other nephrology services for children in these regions.

The paediatric nephrology programmes at these centres have a longstanding nutrition programme, with tube feeding supplementation or gastrostomy feeding introduced if the child is not achieving normal growth. Children with ESRD received early dialysis, beginning when they were not thriving rather than beginning when a set chemical index had been reached.

Table 1 outlines the diagnoses of children with ESRD. No patients were on anticonvulsants, cyclosporin A, FK506, stimulant medication, or growth hormone.

**Procedure**

Parents and participants were fully informed about the nature of the study, which received approval from the Ethics Review Committee of both institutions. Participants completed a half day neuropsychological assessment. For those individuals on haemodialysis, assessments were not carried out on the day they received dialysis treatment. Parents, teachers, and participants each completed behavioural rating scales or self-report questionnaires. Psychological technicians completed the assessment and scoring of the tests without any knowledge of the medical history of the participants.

**Neuropsychological assessment**

Intelligence was assessed using the Wechsler Intelligence Scale for Children–third edition (WISC-III).14 Academic skills were assessed using the Wide Range Achievement Test--
which measures self-esteem.\textsuperscript{24, 25} and adolescents completed Harter's self-report rating scale manuals were used in the analyses. In order to limit the Age standardised scores obtained using the published test and the sibling controls were compared using paired

Ities and behaviour of children with end-stage renal disease Test\textsuperscript{22} were used to assess motor abilities.

The Wide Range Assessment of Memory and Learning\textsuperscript{18} and Learning, Sentence Memory, and Finger Windows subtests of the Expressive One-Word Picture Vocabulary Test.\textsuperscript{20} The Developmental Test of Visual-Motor Integration,\textsuperscript{21} Grooved Pegboard Test,\textsuperscript{22} and Finger-Tapping Tests\textsuperscript{22} were used to assess motor abilities.

There was a trend in the same direction on the measure of fine motor coordination (Grooved Pegboard Test) when patients also had significantly more difficulty on a measure of geometric designs (Developmental Test of Visual-Motor Integration) than their sibling controls (see table 2). ESRD patients had significantly more difficulty copying geometric designs (Developmental Test of Visual-Motor Integration) than their sibling controls (see table 2).

The memory of patients with ESRD and the sibling controls was comparable (see table 2).

The memory tests were lower than the scores of the sibling control group had lower scores than the Brouhard and coworkers used a more limited non-verbal test of intelligence and also found that ESRD patients had lower IQs than sibling controls.\textsuperscript{27} The between group differences in IQ remained significant, even after the ESRD patient, with a full scale IQ of 69, and his sibling were excluded from the analyses. Madden and coworkers found that a group of infants beginning peritoneal dialysis in the first year of life also had a mean IQ in the low average range.\textsuperscript{26}

Despite the frequent absences from school of ESRD patients for medical appointments and treatments, there were no between group differences on measures of academic achievement. Included were measures of achievement in language arts as well as in arithmetic. An important factor in development of reading decoding and spelling abilities is ability to process phonological information.\textsuperscript{29} There were no differences between groups in ability to pronounce phonetically regular nonsense words indicating that the groups had comparable ability to process phonological information. Brouhard and coworkers found that ESRD patients had lower academic achievement than sibling controls. Our cohort of ESRD patients had more success on the same measure of spelling that Brouhard and coworkers used. Our sibling control group had lower scores than the Brouhard and coworkers sample, thus attenuating between group differences, which also helped to explain the discrepancy in findings.

The performance on tests of verbal and non-verbal memory of ESRD patients was comparable to that of sibling controls. We previously reported that children with congenital ESRD had more difficulty on tests of verbal and non-verbal memory than children with acquired ESRD.\textsuperscript{7} This finding suggests that the longer the duration of ESRD, the greater the impact of metabolic disturbances on brain regions responsible for memory. While the scores of the ESRD patients on most of the memory tests were lower than the scores of the sibling controls, the sample was comprised of ESRD patients with either congenital or acquired renal insufficiency, which tended to minimise the patient-control differences.

ESRD patients had more difficulty on tests of motor abilities than sibling controls. They had more difficulty

### Table 1: Diagnoses of patients included in the study

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysplasia + reflux nephropathy</td>
<td>Rapidly progressive glomerulonephritis</td>
</tr>
<tr>
<td>Renal dysplasia + chronic pyelonephritis</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>Cystic dysplasia</td>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Polycystic kidney disease (ARPKD)</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>Megacysts/megareter</td>
<td>Vascular/renal vein thrombosis</td>
</tr>
<tr>
<td>Posterior urethral valves</td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Oligomeganephronia</td>
<td>Renal lymphohemangioima</td>
</tr>
</tbody>
</table>

*Based on biopsy of liver and kidney and family studies.

The Verbal, Performance, and Full Scale IQs of patients with ESRD were in the low average range, but were significantly lower than the IQs of the sibling controls which were in the average range (see table 2). The mean IQs for the siblings were very close to the population normative data, further validating use of siblings as controls.

There were no differences between groups on any of the measures of academic achievement. Included were measures of reading decoding, reading comprehension, spelling, and ability to complete numerical calculations (see table 2). There also were no differences between groups on a measure of ability to process phonological information (Word Attack).

The memory of patients with ESRD and the sibling controls was comparable. The groups did not differ in their ability to immediately recall spoken sentences (Sentence Memory) or to immediately recall visual stimuli (Finger Windows). There was not a difference in their ability to learn and recall a word list over a series of trials (Verbal Learning) or to learn and recall locations of designated targets in a series of visual arrays (Nonverbal Selective Reminding Test).

ESRD patients had significantly more difficulty copying geometric designs (Developmental Test of Visual-Motor Integration) than their sibling controls (see table 2). ESRD patients also had significantly more difficulty on a measure of fine motor coordination (Grooved Pegboard Test) when they used their dominant hand than their sibling controls. There was a trend in the same direction on the measure of non-dominant hand fine motor coordination (see table 2).
accurately copying geometric designs and had more difficulty on a measure of fine motor coordination. With respect to their dominant hand fine motor coordination, the between-group difference was significant, while there was a trend in the same direction on the measure of non-dominant hand fine motor coordination. However, compared to population normative data, their scores on these measures of motor abilities were in the low average to average ranges.

There was no evidence that ESRD patients were exhibiting internalising or externalising behaviour problems. Their self-reported self-esteem was within normal limits, and comparable to that of their siblings.

Lower intelligence could be expected to have negative impact on academic attainment and limit occupational choices. A recent adult outcome study in the Netherlands found that ESRD of childhood is associated with impaired cognitive and educational attainment in adulthood. It is found that ESRD of childhood is associated with impaired cognitive and educational attainment in adulthood.12 It is important to monitor the educational progress of children with ESRD, and to implement appropriate remedial assistance whenever necessary.

The results of this study are encouraging because they showed that children with non-syndromic ESRD did not have any major neuropsychological deficits. They did have more difficulty on measures of intelligence and motor abilities than sibling controls. The findings seem to represent a mild, generalised negative effect on brain functioning which could be the result of a variety of factors including less than optimal nutrition, with resulting impact on growth and development, or consequences of renal treatment, such as method or stability on dialysis, metabolic toxicities, or medication effects. Advances in medical care clearly have improved the outcome for children with ESRD.

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**REFERENCES**

Cerebral palsy, birthweight, and gestation

Both perinatal death and cerebral palsy are more likely in babies whose birthweight is lower than expected for gestational age but data for lower gestational ages are inadequate. Babies whose birthweight is high for gestational age have an increased risk of perinatal death and possibly of cerebral palsy. Babies who grow slowly in utero are more likely to be born early and therefore weight standards based on birthweight may be too low at earlier gestational ages. In a European collaborative study (Stephen Jarvis and colleagues. *Lancet* 2003;362:1106–11, see also commentary, ibid: 1089–90) an attempt has been made to circumvent this difficulty by using fetal growth standards based on ultrasound estimations of weight during pregnancy of healthy babies born at term. Data were gathered from 13 cerebral palsy registers in eight countries of which those from three registers in two countries were excluded from the published analysis. The birthweights and gestational ages of 4503 singleton children with cerebral palsy born between 1976 and 1990 were compared with published reference standards from the North of England and from Sweden. Rates of cerebral palsy were calculated from local population data.

Using weight for gestation standards based on birthweight different patterns were seen for babies born before or after 32 weeks gestation. After 32 weeks rates of cerebral palsy were lowest at a weight for gestation Z score of between 1 and 2 (equivalent to 75th to 90th percentile). There was a reverse-J curve with the highest rates of cerebral palsy at very low and very high Z scores. Before 32 weeks the lowest cerebral palsy rates were at weight for gestation Z scores of between –1 and –2 (about 3rd to 10th percentile). Using fetal growth rate standards this different pattern at earlier gestational ages was no longer seen. (This finding seems difficult to explain and they offer no explanation). Now, at all gestational ages there was the same reverse-J curve with the lowest risk of cerebral palsy at Z scores of between 1 and 2. The findings were similar for all types of cerebral palsy. For babies born between 32 and 42 weeks of gestation, the risk of cerebral palsy was increased 4–6 fold at birthweights below the tenth percentile compared with birthweights between 25th and 75th percentile. For birthweights above the 97th percentile the increase was 1.6-3-1 fold. The optimum birthweight for avoiding cerebral palsy is at 75th to 90th percentile for gestational age (using fetal growth standards at lower gestations). The risk is increased at lighter or heavier birthweights for gestational age. Whether abnormal fetal growth is a cause or a result of cerebral palsy is not known and there is uncertainty about whether the abnormal growth is proportionate (affecting all aspects of growth) or disproportionate (affecting mainly weight). Either way, the abnormal growth starts long before birth.
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