

Behavioral profiles of children with infantile nephropathic cystinosis

Gustavo Delgado MD, Southern California Permanente Medical Group;
Amy Schatz PhD;
Sharon Nichols PhD, Department of Neurosciences, School of Medicine;
Mark Appelbaum PhD, Department of Psychology;
Doris Trauner* MD, Departments of Neurosciences and Pediatrics, University of California, San Diego, School of Medicine, La Jolla, USA.

*Correspondence to last author at Department of Neurosciences, University of California, San Diego, School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093-0935, USA.
E-mail: dtrauner@ucsd.edu

Children with infantile nephropathic cystinosis have evidence of visuospatial and arithmetic deficits on a background of normal intellectual and verbal skills. This study aimed to define further their behavioral phenotype. The Achenbach Child Behavior Checklist was completed by parents of: 64 children and adolescents with cystinosis (33 females, 31 males; mean age 8y 8mo, range 4 to 16y, SD 2y 11mo); 101 healthy controls (47 females, 54 males; mean age 8y 4mo, range 4 to 16y, SD 2y 11mo); 21 children and adolescents with cystic fibrosis (CF), termed chronic-disease controls (9 females, 12 males; mean age 11y 3mo, age range 4 to 17y, SD 3y 5mo). Compared with healthy controls, individuals with cystinosis had evidence of a significantly higher incidence of behavioral problems, including social problems, somatic complaints, and attention problems. Compared with the chronic-disease control group, the cystinosis group differed only on the Social Problems scale, with 22% of participants with cystinosis scoring in the 'at risk' range whereas no participant with CF received an elevated score on this scale. We conclude that children and adolescents with cystinosis have evidence of a significant incidence of social difficulties compared with individuals with another chronic illness and healthy participants. The combination of visuospatial problems, difficulty with arithmetic, attention problems, and social difficulties seen in the cystinosis group constitutes a behavioral phenotype of this genetic disorder. This cluster of cognitive and behavioral symptoms is also seen in the nonverbal learning disabilities syndrome, and suggests a possible early difference in brain development in children with cystinosis compared with children who do not share this genetic disorder.

Cystinosis is an autosomal recessive metabolic disorder in which cystine crystals accumulate in various body tissues including the kidney, cornea, thyroid, and brain (Gahl et al. 2001). The genetic abnormality is a deletion of the *CTNS* gene mapped to chromosome 17p13 (Town et al. 1998). This gene encodes a membrane protein, cystinosin, which is responsible for transporting cystine across the lysosomal membrane. Children develop renal Fanconi syndrome in infancy, and if untreated have renal failure before 10 years of age. With the advent of treatment with oral cysteamine, a cystine-depleting compound, individuals with cystinosis are living longer and healthier lives, and renal failure may be delayed or prevented (Gahl et al. 1987, Markello et al. 1993). This has allowed studies of neurological, cognitive, and behavioral function in individuals with cystinosis (see Trauner et al. 1988, 1989). Trauner et al. (1988) reported that children with cystinosis had normal composite intelligence quotients (IQs) on the Stanford-Binet Intelligence Scale – Fourth Edition (Thorndike et al. 1986) had low scores on the bead memory subtest, suggesting the possibility of specific visual memory deficits. Although intelligence is normal in patients with cystinosis, IQ tends to be somewhat lower than expected compared with parents and siblings (Williams et al. 1994). Academic performance also appears to be adversely affected in some children with cystinosis. Ballantyne et al. (1997) reported that children with cystinosis, compared with normally developing controls, performed significantly lower on tests of arithmetic and spelling than did controls.

Subsequent studies have further defined the nature of the cognitive dysfunction. Deficient performance of patients with cystinosis relative to controls has been demonstrated on tasks involving spatial relations (Trauner et al. 1989), visual motor skills (Scarvie et al. 1996), and tactile perception (Colah and Trauner 1997). Recently, the nature of the visual processing deficit has been more clearly specified (Ballantyne and Trauner 2000). Individuals with cystinosis demonstrate a dissociation in visual processing abilities, with visuospatial functions being significantly more impaired than visual perceptual functions.

So far, only one study has examined the relation between brain structural changes and cognitive performance in cystinosis. Nichols et al. (1990) compared magnetic resonance imaging (MRI) findings with results of cognitive testing in individuals with cystinosis to determine whether cortical atrophy was associated with cognitive impairment. They showed that patients with a greater degree of cortical atrophy had worse performance on a visual short-term memory task.

The presence of specific visual processing and tactile perceptual deficits, and the relatively poorer achievement in arithmetic and spelling, are reminiscent of the pattern seen with nonverbal learning disabilities (NVLDs; Rourke 1982). Children with NVLD typically have difficulty with visuospatial orientation, poor visual memory, and deficiencies in attention to visual and tactile input (Rourke 1988). Such children also have low social competence and difficulty adapting to novel situations, which is often reflected in behavioral problems (Rourke 1989).

Although the cognitive profiles associated with cystinosis have been studied in some detail, the behavioral phenotype (O'Brien and Yule 1995) has not been well characterized. The current study aimed to define better the behavioral patterns of children and adolescents with cystinosis. We used the Achenbach Child Behavior Checklist (CBCL; Achenbach 1991),

See end of paper for list of abbreviations.

to assess various aspects of participant behavior. Because children with cystinosis have a chronic medical condition that may set them apart from other children, it was deemed important to compare the results of the CBCL in individuals with cystinosis not only with healthy controls but also with a chronic-disease control group consisting of children and adolescents with cystic fibrosis (CF). The rationale for choosing this 'chronic-disease' control group was that the demands of CF on social interactions might be similar to those for cystinosis. In both conditions, children require daily medications; both require intermittent hospitalization and, potentially, more frequent absences from school.

Method

PARTICIPANTS

Parents of 186 children and adolescents completed the CBCL. The children included 64 individuals with cystinosis (33 females, 31 males; mean age 8y 8mo, range 4 to 16y, standard deviation [SD] 2y 11mo), 101 typically developing, controls (47 females, 54 males; mean age 8y 4mo, range 4 to 16y, SD 2y 11mo), and 21 children and adolescents with CF (9 females, 12 males; mean age 11y 3mo, range 4 to 17y, SD 3y 5mo). Parents of children and adolescents with cystinosis were either contacted by mail and asked to participate, or asked to complete the CBCL at the annual National Cystinosis Foundation conference. No individual with cystinosis was undergoing dialysis, was in renal failure, or had severe renal insufficiency, at the time the questionnaire was completed. Normally developing controls were recruited from the community over the same time period. At the University of California, San Diego (La Jolla, CA, USA), parents of children with CF were asked to complete the questionnaire during a clinic visit or during their child's hospital admission. Informed consent was obtained in accordance with UCSD Institutional Review Board procedures, and the study complied with the Ethical Principles of the American Psychological Association. Families in all three groups were group-matched for socioeconomic status using the Hollingshead Four Factor Index of Social Status (AB Hollingshead 1975; Yale University, unpublished).

MEASURE

The CBCL was used to assess the sociobehavioral characteristics of children and adolescents in all three groups. The CBCL is a widely used and well-standardized parental report questionnaire for children and adolescents aged 4 to 18 years that has satisfactory validity and reliability (Achenbach 1991).

The CBCL is a 113 item checklist. Each item is scored on a 0 to 2 response scale, where 0=not true, 1=somewhat or sometimes true, and 2=very true or often true. The responses are based on current observations or behaviors observed within the 2 months before completion of the questionnaire. From these items, the following nine behavior problem scales are derived: Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior, and Sexual Problems. An Internalizing score is derived by combining scores from the Withdrawn, Somatic Complaints, and Anxious/Depressed scales, and an Externalizing score is derived by combining the scores on the Delinquent Behavior and Aggressive Behavior scales. A Total Behavior Problems score is derived from the addition of scores on all nine behavior problem scales as well as scores on the items that do not contribute to any of the behavior problem scales (with the exception of the allergy and asthma items, which do not contribute to any scale or the total score). Raw scores are translated to *T* scores, with scores above 70 indicating clinically significant problems, and scores of 67 to 70 representing a 'borderline' clinical range.

ANALYSES

A *T* score of 67 or above on each scale was chosen as an indicator of possible psychosocial problems. For each group, patients were divided into a 'clinically at risk' group and a 'normal' group by using the cutoff score of 67 on each of the scales, and, in addition, two sets of χ^2 analyses were performed to examine differences between the groups. One set examined differences between the cystinosis and control groups. A second set of analyses examined differences between the cystinosis and CF groups.

Table I: Mean (SD) *T* scores of individuals clinically 'at risk' (*T* score \geq 67) on the Child Behavior Checklist (CBCL; Achenbach 1991) scales for cystinosis, cystic fibrosis, and healthy control groups

CBCL scales	Cystinosis (n=64)		Cystic fibrosis (n=21)		Healthy control (n=101)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Withdrawn	54.8 (5.8)	4.6	52.3 (4.2)	0	53.7 (5.1)	3.0
Somatic Complaints	61.2 (8.9)	27.7	55.3 (8.1)	9.5	54.5 (6.1)	5.0
Anxious/Depressed	54.3 (6.1)	6.2	53.3 (5.6)	4.8	53.5 (5.4)	4.0
Social Problems	59 (10.0)	21.5	53.1 (5.4)	0	52.2 (4.6)	2.0
Thought Problems	54.5 (6.8)	9.2	53.3 (5.7)	4.8	52.7 (4.8)	2.0
Attention Problems	56.8 (9.5)	18.5	54.2 (7.3)	9.5	52.0 (4.0)	2.0
Delinquent Behavior	55.0 (6.3)	9.2	52.8 (4.3)	0	52.4 (4.8)	3.0
Aggressive Behavior	56.3 (7.6)	10.8	54.1 (6.2)	9.5	52.0 (3.7)	0
Sexual Problems ^a	51.6 (4.8)	2.0	51.5 (4.7)	0	52.5 (6.2)	4.6
Internalizing	49.4 (10.0)	13.8	48.2 (11.0)	5.0	54.3 (10.0)	4.0
Externalizing	45.7 (9.1)	6.2	48.3 (10.9)	9.5	52.5 (11.1)	2.0
Total Behavior Problems	46.7 (9.5)	20.0	49.3 (10.3)	9.5	55.3 (10.8)	3.0

^aSexual problems are not part of CBCL for children <11 years old (cystinosis n=50, healthy controls n=87, cystic fibrosis n=10).

RESULTS

Table I lists the mean *T* scores and the percentage of children who obtained a *T* score of 67 or above for each of the scales in each of the three groups. Mean *T* scores for all three groups were well within the average range. However, when the percentage of children in each group who scored within the clinically 'at risk' range (*T* score ≥ 67) was taken into account, there were significant differences among groups.

Upon comparison of the cystinosis group with the healthy control group, differences between rates of clinically significant scores were observed on the Total Problems Summary scale (29% cystinosis vs 3% control group; $\chi^2 = 13.17, p = 0.001$) and the Internalizing Problems Summary scale (14% cystinosis vs 4% healthy control group; $\chi^2 = 5.36, p = 0.02$), whereas there was no significant difference between the two groups on the Externalizing Summary scale. Examination of the individual clinical scales also found differences between the cystinosis and control group in rates of scores obtained in the clinically significant range on Social Problems (21.5% vs 2%; $\chi^2 = 17.37, p \leq 0.0001$), Somatic Complaints (27.7% vs 5%; $\chi^2 = 17.14, p \leq 0.0001$), Attention Problems (18.5% vs 2%; $\chi^2 = 13.91, p \leq 0.001$), Thought Problems (9% vs 2%; $\chi^2 = 4.53, p = 0.03$), and Aggression (11% vs 0%; $\chi^2 = 11.36, p = 0.001$; Fig. 1).

Direct comparison of the cystinosis and CF groups revealed that only the Social Problems scale significantly differed between the two chronic-disease groups (21.5% cystinosis vs 0% CF group; $\chi^2 = 5.40, p = 0.025$). Most of the items identified by parents of children with cystinosis as being a problem in the social domain were acting younger than their age, clinging to adults excessively, and preferring to play with younger children.

Discussion

This study demonstrates that children with cystinosis are at higher risk for behavioral difficulties, and, in particular, social

problems, compared with either healthy controls or children with another chronic illness: CF. Although the group means for all scales of the CBCL were within the normal range for all three groups, the percentage of children in the cystinosis group with evidence of social problems was significantly higher than the percentages of children in either the CF or control groups. Children with cystinosis were significantly more likely than healthy controls to have problems related to attention, somatic complaints, and aggression.

The use of a chronic-disease control group allowed us to control for possible nonspecific effects on behavioral and social function of chronic illness alone (Thompson et al. 1987, Mulhern et al. 1989, Gartstein et al. 1999). It may be expected that living with a chronic disease may cause any number of behavioral problems. The pattern seen in the cystinosis group of increased social problems, somatic complaints, attention problems, and aggressive behaviors suggests that these individuals are experiencing more behavior problems than typically developing children. However, when compared with another group of children living with a chronic illness (i.e. CF), children with cystinosis exhibited a significantly higher incidence of social problems only. The Social Problems scale consists of eight items that tap the following areas of the child's behavior or social experience: acts too young for his/her age, clings to adults or is too dependent, does not get along with other children, is teased a lot, is not liked by other children, is overweight, is poorly coordinated or clumsy, and prefers being with younger children (Achenbach 1991). Children with cystinosis tend to be poorly coordinated (Trauner et al. 1988), but this factor alone would not explain the differences in scores found in the current study. Immature behavior (acting younger, clinging to parents and preferring to play with younger children) was more commonly reported in the cystinosis group than in either the CF or control groups. Whether this reflects a neurobiological influence on behavior in cystinosis is unclear. However, previous

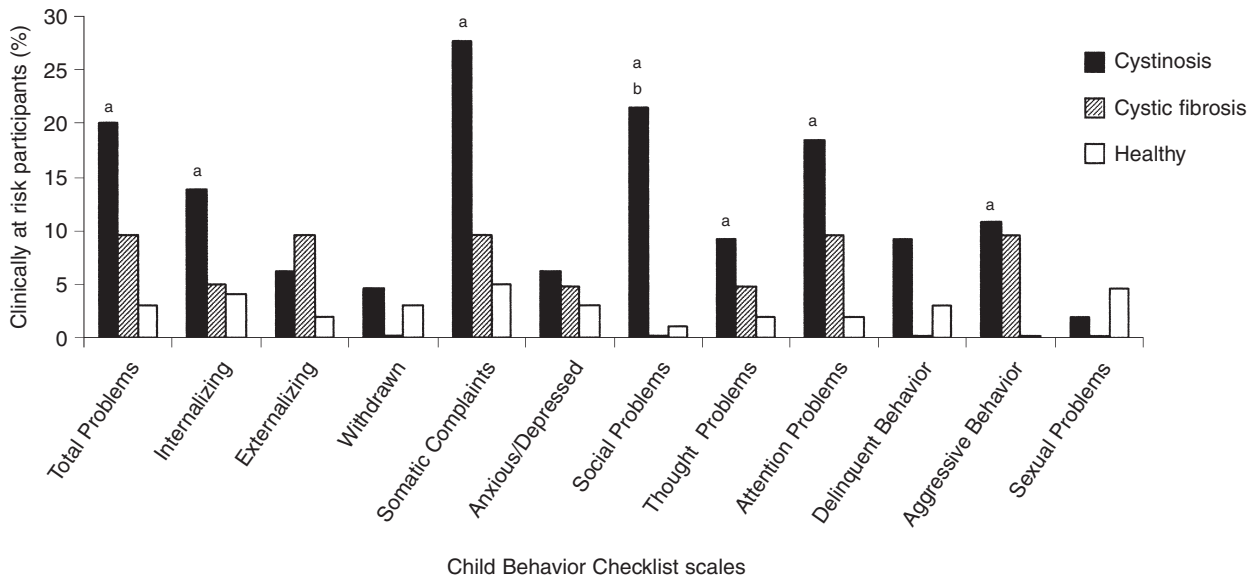


Figure 1: Percentage of individuals in cystinosis, cystic fibrosis, and healthy control groups with *T* scores ≥ 67 for each Child Behavior Checklist scale. ^aSignificant difference between cystinosis and healthy and cystic fibrosis (CF) control groups; ^bsignificant difference between cystinosis and CF groups.

studies using the CBCL showed that participants with CF, when compared with patients with mixed neurological disorders, had significantly lower sociobehavioral morbidity, particularly in the area of social competence (Pumariega et al. 1990). This is in contrast to our findings on children with cystinosis, whose greatest area of difficulty was in social competence.

If the behavioral difficulties observed in children with cystinosis are not solely the result of dealing with a chronic illness, then what other reasons might explain the observed risk for social dysfunction? Possible explanations include damage to neuronal function from cystine accumulation in the brain; a difference in brain development caused by an as yet unknown function of the cystinosis gene; or an effect of one or more of the medications used to treat the symptoms of cystinosis.

Previous studies demonstrating impairments in visual processing (Ballantyne and Trauner 2000), visual memory (Trauner et al. 1988, Nichols et al. 1990), tactile recognition (Colah and Trauner 1997), and arithmetic (Ballantyne et al. 1997), combined with our current findings that children with cystinosis have an increased incidence of social difficulties, suggest that individuals with cystinosis may be manifesting a behavioral phenotype similar to that found in children with NVLDs. Children with NVLD have a pattern of dysfunction which includes problems with tactile perception, visuospatial skills, attention, nonverbal memory, arithmetic, and social competence (Rourke 1982, 1988). Rourke (1989) has suggested that the social deficits observed in individuals with NVLD may be understood by using a cognitive–developmental model. Early learning is dependent on sensorimotor functioning, i.e. learning through touch, vision, and movement. However, children with NVLD, as well as children with cystinosis, have been shown to have specific deficits in visuospatial and tactile skills. Social interaction, in particular, relies on the perception, evaluation, and application of nonverbal cues, which have been found to be deficient in children with NVLD (Rourke 1989). As such, children with NVLD may be expected to withdraw from social situations and become socially isolated, which may result in social problems similar to those pinpointed in children with cystinosis in the present study.

Rourke (1989) postulates that damage to or deficiency in white matter early in development may account for the NVLD syndrome. Interestingly, MRI studies of children and adults with cystinosis demonstrate primarily abnormalities of white matter (Nichols et al. 1990, Hodge et al. 1992). Although the cause of the changes to white matter in cystinosis is unknown, these abnormalities may be present even in young children, and suggest that there may be an early difference in myelination, perhaps caused by the metabolic abnormalities. Such an early disruption in brain myelination could account for the differences in cognitive function observed in individuals with cystinosis.

All of the individuals participating in this study were receiving cysteamine treatment, and none had significant renal dysfunction or metabolic derangements at the time of the study. Because of this fact, it was decided not to use children with chronic renal failure as a chronic-disease control group. Children in the latter group may be undergoing frequent dialysis and have metabolic disturbances, such as uremia, which might result in behavioral disturbances (Fielding et al. 1985; Eisenhauer et al. 1988; Reynolds et al. 1990, 1991; Davis et al. 1996; Park et al. 1996).

It is difficult to determine the effect that cysteamine therapy

has on neurocognitive complications in cystinosis. At present, most children with cystinosis have been taking this cystine-depleting drug from early life. The potential effects on long-term neurobehavioral function as a result of reducing cystine accumulation are unknown. One limited retrospective study showed a reversal of brain computed tomography scan abnormalities and resolution of neurological symptoms in two out of four patients treated with cysteamine over a period of months to years (Broyer et al. 1996). It is possible that our population with cystinosis might have had more severe behavioral dysfunction without the benefit of cysteamine therapy.

There are several possible confounding factors in interpreting the data from the present study. Perhaps there is a greater psychosocial consequence of disease manifestations in patients with cystinosis than those with CF, which results in lower social competence. For instance, increased urinary frequency, common to patients with cystinosis, may influence social development more than dealing with shortness of breath or pulmonary infections in patients with CF. Further, some authors have cautioned about the use of the CBCL in children with chronic illnesses, as certain items that refer to medical diagnoses or physical symptoms might erroneously be attributed to behavioral problems when they could be a manifestation of side effects from medication or directly from the medical condition (Perrin et al. 1991). Of the items on the CBCL, there are only a few questions that directly relate to illness or medication, rather than the actual behavioral problems (e.g. pain in eyes or stomach, being tired or dizzy). By including a chronic-disease control group, we have aimed to account for any items that may be endorsed purely on the basis of having a chronic illness. The fact that the two chronic-disease groups differ only on the Social Problems scale is strong evidence that individuals with cystinosis have social difficulties that cannot be accounted for solely on the basis of having a chronic illness.

Despite the questions raised above, the present study does demonstrate a high incidence of social problems in children with cystinosis compared with individuals with CF and with controls. The underlying reasons for this finding remain to be determined, but the pattern of cognitive and behavioral deficits observed in cystinosis appears to constitute a behavioral phenotype for this genetic disorder. Future studies of behavior and cognition in children with cystinosis variants, who have different genetic alterations, will help to better determine how specific this behavioral phenotype is to the 17p13 deletion.

DOI: 10.1017/S0012162205000782

Accepted for publication 10th August 2004.

Acknowledgments

This work was supported by grant RO1 HD23854 from the National Institutes of Health (DA Trauner, PI), and by a gift from the National Cystinosis Foundation to Dr Trauner. The authors thank the children with cystinosis, and their families, for their participation in this study, and for their ongoing support of our research. We thank Dr Michael Light and Dr Mark Pian for their help in recruiting patients with CF, the patients with CF and their families for their willingness to participate, and Dr Angela Ballantyne for reviewing the manuscript.

References

- Achenbach TM. (1991) *Manual for the Child Behavior Checklist 4-18*. Burlington, VT: Department of Psychiatry, University of Vermont.
- Ballantyne AO, Scarvie KM, Trauner DA. (1997) Academic achievement in individuals with infantile nephropathic cystinosis. *Am J Med Genet* **74**: 157-161.
- Ballantyne AO, Trauner DA. (2000) Neurobehavioral consequences of a genetic metabolic disorder: visual processing deficits in infantile nephropathic cystinosis. *Neuropsychiatry Neuropsychol Behav Neurol* **13**: 254-263.
- Broyer M, Taete MJ, Guest G, Berthaelaemae JP, Labrousse F, Poisson M. (1996) Clinical polymorphism of cystinosis encephalopathy: results of treatment with cysteamine. *J Inherit Metab Dis* **19**: 65-75.
- Colah S, Trauner DA. (1997) Tactile recognition in infantile nephropathic cystinosis. *Dev Med Child Neurol* **39**: 409-413.
- Davis MC, Tucker CM, Fennell RS. (1996) Family behavior, adaptation, and treatment adherence of pediatric nephrology patients. *Pediatr Nephrol* **10**: 160-166.
- Eisenhauer GL, Arnold WC, Livingston RL. (1988) Identifying psychiatric disorders in children with renal disease. *South Med J* **81**: 572-576.
- Fielding D, Moore B, Dewey M, Ashley P, McKendrick T, Pinkerton P. (1985) Children with end-stage renal failure: psychological effects on patients, siblings and parents. *J Psychosom Res* **29**: 457-465.
- Gahl WA, Reed GF, Thoene JG, Schulman JD, Rizzo WB, Jonas AJ, Denman DW, Schlesselman JJ, Corden BJ, Schneider JA. (1987) Cysteamine therapy for children with nephropathic cystinosis. *N Engl J Med* **316**: 971-977.
- Gahl WA, Thoene J, Schneider JA. (2001) Cystinosis: a disorder of lysosomal membrane transport. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B, editors. *The Metabolic and Molecular Basis of Inherited Disease*. 8th edn. New York: McGraw-Hill. p 5085-5108.
- Gartstein MA, Short AD, Vannatta K, Noll RB. (1999) Psychosocial adjustment of children with chronic illness: an evaluation of three models. *Dev Behav Pediatr* **20**: 157-163.
- Hodge BL, Hesselink JR, Trauner DA. (1992) MRI study of white matter changes in cystinosis. *Society Neurosci Abstr* **18**: 333. (Abstract)
- Markello TC, Bernardini IM, Gahl WA (1993) Improved renal function in children with cystinosis treated with cysteamine. *N Engl J Med* **328**: 1157-1162.
- Mulhern RK, Wasserman AL, Friedman AG, Fairclough D. (1989) Social competence and behavioral adjustment of children who are long-term survivors of cancer. *Pediatrics* **83**: 18-25.
- Nichols SL, Press GA, Schneider JA, Trauner DA. (1990) Cortical atrophy and cognitive performance in infantile nephropathic cystinosis. *Pediatr Neurol* **6**: 379-381.
- O'Brien G, Yule W. (1995) *Behavioural Phenotypes*. *Clinics in Developmental Medicine No. 138*. London: Mac Keith Press.
- Park CH, Kim DY, Kim KS, Cho WH, Park SB, Kim HC. (1996) Clinical and psychosocial consequences of renal transplantation in children. *Transplant Proc* **28**: 1604-1606.
- Perrin EC, Stein REK, Drotar D. (1991) Cautions in using the Child Behavior Checklist: observations based on research about children with a chronic illness. *J Pediatr Psychol* **16**: 411-421.
- Pumariega AJ, Breiger D, Pearson D, Dreyer C, Seilheimer DK. (1990) Behavioral symptoms in cystic fibrosis vs. neurological patients. *Psychosomatics* **31**: 405-409.
- Reynolds JM, Garralda EM, Postlethwaite RJ, Jameson RA. (1990) Psychosocial issues in children on hospital haemodialysis: nurses' views. *Pediatr Nephrol* **4**: 176-177.
- Reynolds JM, Garralda EM, Postlethwaite RJ, Goh D. (1991) Changes in psychosocial adjustment after renal transplantation. *Arch Dis Child* **66**: 508-513.
- Rourke BP (1982) Central processing deficiencies in children: toward a developmental neuropsychological model. *J Clin Neuropsychol* **4**: 1-18.
- Rourke BP (1988) Syndrome of nonverbal learning disabilities: developmental manifestations in neurological disease, disorder, and dysfunction. *Clin Neuropsychol* **2**: 293-330.
- Rourke BP (1989) *Nonverbal Learning Disabilities: The Syndrome and the Model*. New York: The Guilford Press.
- Scarvie KM, Ballantyne AO, Trauner DA. (1996) Visuomotor performance in children with infantile nephropathic cystinosis. *Percept Mot Skills* **82**: 67-75.
- Thompson KL, Varni JW, Hanson V. (1987) Comprehensive assessment of pain in juvenile rheumatoid arthritis: an empirical approach. *J Pediatr Psychol* **12**: 241-255.
- Thorndike R, Hagan E, Sattler J. (1986) *Stanford-Binet Intelligence Scale*. 4th edn. Chicago: Riverside Publishing.
- Town M, Jean G, Cherqui S, Attard M, Forestier L, Whitmore SA, Callen DE, Gribouval O, Broyer M, Bates GP, van't Hoff W, Antignac C. (1998) A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. *Nature Genet* **18**: 319-324.
- Trauner DA, Chase C, Scheller J, Katz B, Schneider JA. (1988) Neurologic and cognitive deficits in children with cystinosis. *J Pediatr* **112**: 912-914.
- Trauner DA, Chase C, Ballantyne A, Tallal P, Schneider J. (1989) Patterns of visual memory dysfunction in children with cystinosis. *Ann Neurol* **26**: 436. (Abstract)
- Williams BLH, Schneider JA, Trauner DA. (1994) Global intellectual deficits in cystinosis. *Am J Med Genet* **49**: 83-87.

List of abbreviations

CBCL	Achenbach Child Behavior Checklist
CF	Cystic fibrosis
NVLD	Nonverbal learning disabilities
