CYSTINOSIS
AND THE BRAIN

Doris A. Trauner M.D.
Professor, Departments of Neurosciences and Pediatrics
University of California San Diego School of Medicine
La Jolla, California USA
Rady Children’s Hospital San Diego
San Diego, California USA
TABLE OF CONTENTS

I. Background: Why is the Brain Involved in Cystinosis? .................................1

II. Neurological Problems in Cystinosis...............................................................4
   a. Motor Function in Cystinosis..................................................................4
      i. Gross Motor.......................................................................................4
      ii. Fine Motor .....................................................................................5
      iii. Visual Motor ................................................................................5
      iv. Oral Motor ....................................................................................5
   b. Seizures ...................................................................................................6
   c. Idiopathic Intracranial Hypertension (IIH)
      (Pseudotumor Cerebri).......................................................................6

III. Cognitive Function in Cystinosis .................................................................8
   a. General Intelligence............................................................................8
   b. Visual Perception, Visual Spatial Function
      and Visual Memory...........................................................................9
   c. Academic Issues in Cystinosis ...........................................................10
   d. Other Cognitive Issues.......................................................................11
   e. Non-Verbal Learning Disability (NVLD) in Cystinosis......................12
   f. Potential Causes for Cognitive Dysfunction in Cystinosis .................12

IV. Behavioral Issues in Cystinosis .................................................................13

V. Late-Onset Encephalopathy/Dementia .......................................................15

VI. Myopathy ..................................................................................................16

VII. Interventions for the Neurological and Cognitive Complications of Cystinosis

VIII. Conclusions ............................................................................................19

IX. Bibliography ..............................................................................................20

Acknowledgements

The research from Dr. Trauner's laboratory that was reported in the book was funded
by the National Institutes of Health HD023854, and by grants from the Cystinosis
Foundation, the Cystinosis Research Foundation and the Cystinosis Research
Network. None of the work would have been possible without the generous
participation of the children and adults with cystinosis and their families.

Author Contact Information

Doris Trauner M.D.
University of California San Diego School of Medicine
9500 Gilman Drive, La Jolla, CA 92093–0935 USA
dtrauner@ucsd.edu
Nephropathic cystinosis is a genetic condition. It is in a group of disorders called lysosomal storage diseases. The lysosomes are small membrane-bound structures that are found inside of every cell in the body (See Figure 1 for a diagram of a typical cell with intracellular structures). Lysosomes act to clear unwanted “debris” from the cell.

Cystine is an amino acid that is in the lysosome because of the normal breakdown of proteins that takes place as part of a complex process of chemical events that keep the body healthy. The gene in cystinosis that is abnormal codes for a protein called cystinosin. This protein acts as a carrier to transport cystine across the lysosomal membrane to get out of the lysosome and get cleared from the cell. If the transport mechanism is not working properly because of the defective gene, cystine accumulates in the lysosomes and causes damage to the cells.

**Figure 1. Diagram of a mammalian cell showing intracellular structures, including lysosomes**

**Cell Structure**

- Cilia
- Lysosome
- Centrioles
- Microtubules
- Golgi apparatus
- Smooth endoplasmic reticulum
- Mitochondrion
- Rough endoplasmic reticulum
- Cell membrane
- Cytoplasm
- Nucleolus
- Chromatin
- Ribosomes
- Nuclear membrane

Cell damage may occur in any organ in the body. In cystinosis, the kidney is the earliest and most severely affected organ. Kidney disease starts early, in the first year of life, with excessive urination, nausea, vomiting, poor growth, and problems with the bones (a form of rickets). If the condition goes untreated, children will have kidney failure by the age of 10 years, and will need a kidney transplant. Fortunately, a successful treatment has been found, in the form of a medication called cysteamine (Cystagon). This medication can slow the progress of the kidney disease tremendously, such that many individuals with cystinosis can grow normally and the need for a kidney transplant can be delayed for many years, with some individuals not needing a kidney transplant even into their teens and early adult life.

Although the kidney is the most obviously affected organ in cystinosis, it is not the only part of the body that can be damaged. Brain involvement in cystinosis has been known for over 40 years, although the functional consequences of that have only become clear over the past 2 decades. The earliest reports of brain involvement were from autopsy studies of children who died with cystinosis. In those reports, mostly from the 1950s, cystine crystals were detected in the choroid plexus, pineal gland, and meninges of the brain. The choroid plexus is outside the brain itself, but its function is to re-absorb cerebrospinal fluid so that excess fluid does not accumulate in the brain. It was suggested, based on the presence of cystine in the choroid plexus, that perhaps children with cystinosis might have excess fluid accumulation in the brain, or hydrocephalus. This was relevant to later reports of abnormal brain scans in children with cystinosis (see below). Several decades later, cystine crystals were reported in brain cells, in a case report by Ross et al. (1982) in which a brain biopsy was performed on a child with cystinosis who had developed seizures and cognitive decline. Another autopsy case report in 1982 of a 20-year-old cystinotic adult who had died of accidental drowning identified what appeared to be progressive damage to the white matter of the brain (Levine & Paparo). Similar white matter shrinkage and damage to the nerve sheaths (demyelination) were reported in a 28-year-old man with cystinosis who died after a lengthy neurological illness with severe cognitive decline. (Vogel et al., 1990). Jonas et al. (1987) conducted an autopsy on a 25-year-old woman who had died of renal failure from cystinosis. They measured tissue cystine levels in multiple organs, and found the brain levels of cystine to be markedly elevated compared with levels measured in brains of individuals without cystinosis who had died of accidental causes.

Although the information on brain pathology is somewhat limited, it is clear from every case studied that at least prior to the advent of therapy with cysteamine, there were abnormalities in the brains of individuals with cystinosis. In addition, neuro-imaging studies have consistently demonstrated structural differences in the brains of individuals with cystinosis. Ehrich et al. (1979) reported brain atrophy, or smaller brains, in children with cystinosis using computerized tomographic (CT) scans. They compared the CT scans of the children with cystinosis to those of children with chronic renal failure from other causes, and noted definite differences between the 2 groups. They hypothesized that the metabolic defect, still unknown at the time, might be responsible for shrinkage of the brain in cystinosis. Ross et al., in 1982, described a child with cystinosis who had “nonabsorptive” hydrocephalus on CT scan. This child received a shunt to drain fluid from inside her brain, and her intellectual function was said to have improved greatly after shunt placement. However, these early studies were hindered by low numbers of patients (often only 1 or 2) and by the fact that the children had major complications from their kidney disease. By 1986, when kidney transplant had become increasingly and successfully performed for renal failure, Cochat et al. also reported cerebral atrophy in cystinosis patients compared with patients with other causes of renal failure, and concluded that individuals with cystinosis would have cortical and subcortical brain atrophy by 10-20 years of age.

More recent neuro-imaging studies conducted in the era of cysteamine therapy will be discussed later.

The cause of the brain abnormalities has not
been completely clarified. Accumulation of cystine crystals was not sufficient to explain all of the pathological changes seen in the brains of autopsied patients. The neuro-pathological and neuro-imaging findings were not similar to what was seen in patients with kidney disease of other causes, suggesting that the brain changes were related specifically to cystinosis. Whether cysteamine treatment prevents these changes remains to be determined.

We have conducted our own neuro-imaging studies on children with cystinosis, ages 2-17 years, using a 1.5 Tesla MRI scanner and a standard research protocol. All of the children scanned have been on cysteamine treatment from early life, and none were of scanning and the presence or absence of volume loss, and abnormal findings were present even in some young children. Thus, it appears that there is a very early effect on brain development in almost half of the children with cystinosis that results in early structural changes that can be seen on MRI scanning. At this point it is not clear why only some individuals with cystinosis have changes in brain structure, but this is an important unanswered question.

Despite the fact that pathological changes were known to occur in the brains of people with cystinosis, until the kidney disease could be more effectively treated, the clinical implications of these findings, specifically neurological complications, were not recognized. The only exception was a severe progressive neurological condition associated with dementia (see below). With better treatment, it has now become apparent that many individuals with cystinosis do have milder neurological problems, and that in some instances these can negatively affect quality of life and academic success.

Figure 2. Magnetic resonance imaging (MRI) brain scan of a healthy child (left) and a child with cystinosis (right) both age 4 years. Note on the MRI of the cystinosis child, the dark areas (ventricles) inside the brain are larger than the ones on the left, reflecting loss of brain volume in the cystinosis brain.
The nervous system consists of the brain, spinal cord, nerves and muscles of the body. The brain is responsible for virtually everything we do — including thinking, speaking, moving, feeling, hearing, seeing, and learning. When any part of the brain is not working properly, any or all of these functions can be disrupted to some extent. Some of these functions can be impaired in individuals with cystinosis. We will discuss each area of function separately.

It is important to recognize that not every person with cystinosis will experience any or all of the problems in neurological function to be discussed. Wherever possible, the incidence of each type of abnormality will be specified.

A. MOTOR FUNCTION IN CYSTINOSIS

Motor function refers to strength and coordination of all groups of muscles, such that a person is able to walk, run, jump, hop and skip (gross motor skills) and use their hands to manipulate objects, for example to feed themselves with a fork, button clothes, tie shoes, color within the lines, and hold a pencil to write (fine motor skills). Motor function can be impaired for several reasons:

1) the cortex of the brain may not be able to communicate adequate signals to the muscles to allow them to function properly;
2) the lower parts of the brain (e.g., the brainstem and cerebellum) may alter the strength or the tone of the muscle so that the muscles aren’t able to function as well;
3) the spinal cord may not be able to send signals to the muscle and the muscle becomes weak or is either too stiff or too floppy to function properly;
4) the nerves to the muscles may not function to send normal signals to the muscle to contract and relax when necessary; or
5) the muscles themselves may be weak and not able to maintain the strength needed to perform normal functions.

i. Gross Motor
The earliest motor problems seen in cystinosis are likely related to the kidney disease. Infants with cystinosis may have delays in their motor development, and be late to sit up and walk. This is true particularly when they are not diagnosed until later than 1 year of age. They may develop rickets, which further complicates walking because of bony deformities. However, even in children who are being treated with cysteamine, a significant number (50% or more) will have gross motor dysfunction. This mainly shows itself as motor coordination and balance issues, such as with hopping, skipping, and walking on a balance beam. Gross motor problems are very prevalent in children with cystinosis between 1 and 5 years of age. After that, there seems to be an improvement, and gross motor skills often normalize by school age and are not likely to cause any obvious problems for the older cystinosis child. In fact, some children and adolescents with cystinosis develop into good athletes.
Along with motor coordination and balance problems, many children with cystinosis have low muscle tone in the first few years of life. Tone is the amount of resistance that a muscle has at rest. Even when a muscle is completely relaxed, there is some tone in the muscle. If muscle tone is too low, it may show up as walking on flat feet, bowing of the knees backward when standing, and protruberant abdomen (belly sticking out) from poor tone in the abdominal muscles. Although low muscle tone in itself is not a serious problem, it may affect posture and coordination.

ii. Fine Motor

Fine motor skills are also problematic for about 40% of children with cystinosis. This does not generally cause obvious problems as toddlers. However, by 3 years of age there may be clear difficulties with drawing, copying, and fine motor movements such as cutting with a scissors or buttoning clothes. Hand coordination continues to be deficient in these same individuals as they go into school. When this occurs, they may have difficulty with drawing, using a scissors, manipulating small objects, and writing.

iii. Visual Motor

Eye-hand (visual motor) coordination is one of the most persistent areas of deficiency in individuals with cystinosis, and may be seen even in some adults with this condition. When such problems persist, using a computer to do written work may help to minimize the consequences of visual motor incoordination.

Visual motor function is essentially the same as eye hand coordination. Good visual motor skills are required to color within the lines, to draw and to write. In young children, we can assess visual motor function by having them color a picture or trace a shape. As children advance into kindergarten, they learn to print their name, the alphabet, and then words. Visual motor function is impaired in approximately 40% of individuals with cystinosis. This is true in young children, but also in older children and adults. It does not get better with time in most instances. We have found visual motor impairment in children who were treated from early life with cysteamine, suggesting that the visual motor problem is caused by very early, possibly even prenatal, changes in the brain. See Figure 3, below, for an example of drawing problems in a child with cystinosis.

Figure 3. Copies of a figure from the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI), 5th Edition, by 2 typical 6 year old children and one child with cystinosis of the same age. Note the inversion of the arrow heads in the drawing by the child with cystinosis.

iv. Oral Motor

Using the muscles of the face, mouth, tongue and throat requires good oral motor function. If oral motor skills are impaired, children or adults may have difficulty chewing or swallowing food. They may also have problems speaking and articulating words.

In cystinosis, there are 2 types of oral motor problems that can occur. The first is evident very early in life, and consists of difficulty with chewing and swallowing. At times the problem may be so severe that the infant is unable to eat or drink anything orally, and must have a device called a gastrostomy tube (g-tube) inserted through the skin and into the stomach in order to feed the child adequately to maintain normal nutrition. The child may require g-tube feedings for years. Most children eventually are able to eat and drink by mouth.

The second type of oral motor problem occurs later in life, usually in the late teens to twenties. In this situation, there is a progressive muscle weakness that evolves over the course of several years, and consists of a particular pattern of muscle weakness that starts in the hands, moves to the shoulders, and early on involves the muscles of the lower face and mouth. Adults with cystinosis myopathy have progressively more severe problems with chewing and swallowing food, and may choke on foods repeatedly. They also have increasing difficulty with both the volume and articulation of speech, and develop a hyper-nasal pattern of speech from weakness of the palate. This may make it difficult for them to be understood by others. There currently is no effective treatment for cystinosis myopathy. Although some experts believe that early treatment with cysteamine may prevent the myopathy from developing, adults who have maintained excellent compliance with cysteamine therapy for many years still may exhibit symptoms of muscle disease, indicating that cysteamine alone may not prevent the myopathy from developing.

B. SEIZURES

Another neurological complication of cystinosis is seizures. Seizures are the result of abnormal irritative electrical discharges in the brain. There are many types of seizures, including grand mal seizures or convulsions, partial onset seizures where there may be awareness during the seizure but loss of motor control, or absence-like seizures (petit mal) where the person is observed to “space out” briefly with no awareness during the episode. Case series of patients with cystinosis who had seizures have been reported since the 1970s. Most of the reported cases have had grand mal seizures or convulsions. However, other patients have reported absence or petit mal-type seizures.

The prevalence of seizures in cystinosis patients is not known. Recurrent unprovoked seizures, or epilepsy, has a prevalence of approximately 1% of people of all ages in the United States. Unprovoked seizures means that there was no clear precipitating cause for the seizure, such as head trauma or high fever and/or the individual was outside the age range for febrile seizures (6 months to 5 years of age). Wolff et al. (1982) reported that 6 of the 12 cystinosis patients they studied had more than one seizure, and that they could not find a clear reason for the seizures in some of the cases. In another study of 19 patients with cystinosis prior to cysteamine availability, 5 of the patients (roughly 25%) studied had a history of seizures (Broyer et al., 1987). However, this was a small number of total patients and the seizures may have been related to other factors such as electrolyte (salt) imbalance and other chemical imbalances in the body caused by dialysis and kidney failure. Recently, the Cure Cystinosis International Registry has accumulated information from almost 300 individuals with cystinosis. In this very large sample, 8% of patients had experienced seizures, making the prevalence at least 8 times more common than expected in the general population.

Seizures in cystinosis may occur at any age, although most begin in the teens or in adult life.
No specific metabolic abnormality has been associated with seizure onset, and it is unclear what the underlying cause or triggering events might be. It is important to treat recurrent unprovoked seizures because seizures can cause further neurological problems, particularly if there are many seizures. Also, if a person has untreated seizures they are unable to drive a car or do certain jobs. Treatment of seizures consists of anti-seizure medications, but treatment is complicated by concerns about medication interactions and potential adverse effects on kidneys. Several newer anticonvulsant medications appear to be safe to use in this type of situation, in that they do not cause kidney damage and can be taken safely in the presence of lowered kidney function.

C. IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH) (PSEUDOTUMOR CEREBRI)

Idiopathic Intracranial Hypertension (IIH), also known as pseudotumor cerebri or Benign Intracranial Hypertension, is a condition in which there is an increase in pressure in the brain (increased intracranial pressure). This happens in the absence of excess fluid, such as is found in hydrocephalus, and also in the absence of a mass lesion such as a tumor or blood clot. This condition can begin at any time during childhood or adult life. The most prominent and consistent symptom is headache, although other associated symptoms may include double vision, blurred vision, ringing in the ears, nausea and/or vomiting. The most serious potential complication is loss of vision. This is due to constant and prolonged pressure on the optic nerve from the increased intracranial pressure. IIH can occur at any age, although it is rare in infants. Women develop it more often than men, and obesity has been linked to it as a causative factor. IIH can also develop as the result of exposure to certain medications, including some antibiotics (such as tetracycline, minocycline, and sulfas medications); steroids; Vitamin A; cyclosporine; and birth control pills. Certain medical conditions, including kidney failure and hormonal disorders, have also been associated with IIH. In 2004, Dogulu et al. reported 8 cases of IIH in children and young adults with cystinosis. Six of the eight patients were taking medications known to be associated with IIH. All cases had total recovery with the exception of one patient who sustained visual impairment. The number of cases exceeds what would be expected in the general population, suggesting that either cystinosis itself, or one of the treatments for cystinosis, make the person at higher risk for developing IIT.

Diagnosis of IIH is made on the basis of an examination of the eyes that shows swelling of the optic nerve in the back of the eye, and a brain scan (either MRI or CT scan) that shows no evidence of tumor, bleed, clot, or other mass lesion and no evidence of hydrocephalus. A spinal tap showing increased pressure confirms the diagnosis, and also rules out other causes for the increased pressure such as infection. Treatment is aimed at reducing the pressure with fluid-reducing medications such as acetazolamide. At times treatment with a steroid such as prednisone is required to reduce pressure. Repeated spinal taps can control pressure for a while and are particularly important in relieving pressure on the optic nerve. Most cases of IIT resolve within 6 months, after which no further treatment is required. Rarely, surgery to relieve the pressure, usually in the form of a shunt from the spinal canal to the abdomen, is needed. An alternative surgical technique is optic nerve sheath fenestration, which can relieve the pressure on the optic nerve and preserve vision.
Until the kidney problems in cystinosis were able to be controlled with some success, little attention was paid to other organs in the body. Once kidney problems could be treated and children were living longer and healthier lives, it became apparent that there might be problems in other areas. One of the least recognized but potentially problematic areas is that of cognitive dysfunction.

Cognition is a broad concept that encompasses the mental process of knowing. This includes many skills, such as awareness, perception, communication, processing of external stimuli (for example, what one hears or sees), reasoning, and judgment.

For many years it was thought that children with cystinosis had normal cognition. Wolff et al. in 1982 reported on psychosocial and intellectual development in 12 children with cystinosis. Most of the children were in kidney failure, yet despite that, all but one was found to have intelligence (IQ) in the normal or above average range, and all were said to be doing satisfactorily academically, although no formal academic testing was reported.

The initial reports of a potential difference in cognitive performance came in 1988, when we described a specific area of relative weakness in visual memory. The first study (Trauner et al., 1988) included 22 children and young adults with cystinosis. We reported then, and confirmed in later studies, that general intelligence is normal in people with cystinosis. Speech and language skills are also normal, with the exception of the late-onset speech problems related to muscle weakness. However, a series of studies have demonstrated a specific cognitive profile that highlights a deficiency in visual spatial skills and visual spatial memory in approximately 40-50% of children and adults with cystinosis. Since then, we have expanded our knowledge of the cognitive deficits in cystinosis. In general, both children and adults with cystinosis may show difficulties with visual spatial, visual motor, and visual memory tasks. They also may have difficulty with mental imagery and mental rotation. Each of these will be described in more detail along with the relevance of each skill to everyday functioning.

A. GENERAL INTELLIGENCE

As mentioned above, Wolff et al. (1982) reported that the 12 children with cystinosis that he had studied had normal intelligence. The IQ levels ranged from 72 to 143. Ten of the 12 children had IQ scores that were well within the population mean of 100 with a standard deviation of ± 15 for the test used. That study did not compare the IQs of the cystinosis group with those of any other group. Subsequently, Williams et al. (1994) reported on IQ in 15 cystinosis patients, 23 unaffected siblings, and 24 parents of the cystinosis patients. They as well found that overall intelligence was within the normal range, with a mean IQ of 96 for the cystinosis group. However, this study went further and conducted IQ testing on other unaffected family members of the cystinosis patients. When compared with their parents (mean IQ 105) and unaffected siblings (mean IQ 107), the cystinosis patients actually had lower IQs than would be predicted by the scores of other family
Cystinosis and the Brain

The study concluded that while individuals with cystinosis have generally normal intelligence, there is a subtle lowering of IQ likely caused by the cystinosis, although other causes for the observed changes, such as kidney problems or medication effects, could not be completely ruled out. Subsequent studies have consistently found normal intelligence in almost all children and adults with cystinosis.

B. VISUAL PERCEPTION, VISUAL SPATIAL FUNCTION AND VISUAL MEMORY

Visual perception refers to the ability to perceive and process information about an object or scene by observing it with the eyes. For example, when someone looks at a photograph, they perceive familiar and unfamiliar faces, can describe the scene, name objects in the photo, and provide other details of what they perceived by visual examination of the photo. Visual spatial function refers to the ability to perceive where objects are in space when viewed with the eyes. As an example, when reading a map of the United States, the person has to be able to determine which direction is north, south, etc., as well as where Illinois is located with respect to Michigan. These are spatial associations that require intact visual spatial processing. Visual memory refers to the ability to retain visual information after it is gone, so that the information can be recalled when necessary. Finding one’s car in a parking lot, or remembering where the car keys are, often utilizes visual memory.

Children and adults with cystinosis have a dissociation between visual perception and visual spatial function. That is, they are good at visual perceptual skills, such as identifying an object by viewing a line drawing of parts of the object. They have no difficulty identifying pictures of objects, naming colors or shapes. However, when there is a spatial component to the task, we see in about half of children with cystinosis, difficulty with the spatial components of the task. So, for example, if a person with cystinosis is asked to follow a simple map, or mentally rotate a shape in their mind to see if it matches another shape, they have difficulty with successfully accomplishing that task. We have now tested approximately 100 children and young adults, starting at age 3 years, with nephropathic cystinosis, as well as an even larger number of children without cystinosis who were matched on gender and age to the cystinosis group, and have consistently found the same dissociation: visual perception is normal, but visual spatial skills are below expected for age.

Having to remember where an object is in space is even more challenging than having to perform a visual spatial task with the item in front of the person. Visual memory is the capacity to remember things previously seen but no longer there. Visual spatial memory is also problematic for many individuals with cystinosis. If they are asked to mentally picture and remember where an item was on a page they had previously been shown, they may have difficulty remembering the location. Having to remember such information may bring out the visual spatial problem even more, because of the added memory component.

Since many children with cystinosis have visual spatial problems, we decided to look at their ability to learn given visual or verbal information. We used a well-known verbal learning test, the California Verbal Learning Test, to test verbal learning. In this test, the person is given a list of items and is required to learn them over 5 trials. There is then a delay after which they are asked to remember the items they learned. We then developed a visual learning task that was as close to the verbal learning test as possible, also using 5 trials but using visual designs that could not be given a name to help with remembering them. We found that children and adults with cystinosis did well on verbal learning, but were slow at visual learning.

From this, as well as another related study, we determined that one of the problems with visual learning and memory relates to slower than normal processing of visual information. That is, it takes the brain longer to register what it sees in a person...
with cystinosis compared with a similar-aged person without cystinosis. As with all of the other studies, this does not apply to every individual with cystinosis, but is a common enough finding that it should be considered in a person with cystinosis who is experiences problems that might be related to visual learning and memory.

How does a problem with visual spatial skills and spatial memory affect someone in everyday life? Most of us don’t realize how important such a skill is. But consider some of the examples already given: reading a map; finding your way in a strange place such as a shopping mall; remembering where you left something in your room. And for a school-age child, learning simple arithmetic may be challenging because of visual spatial problems. This will be discussed further below.

C. ACADEMIC ISSUES IN CYSTINOSIS

Many children with cystinosis (about 30–40%) experience difficulty in school with one or more academic subjects. In the past it was assumed that school problems were related to missing a lot of school due to medically related issues such as doctor’s visits and hospitalizations. Now, however, most children with cystinosis miss very little school because medications help them to remain healthy. Despite that, there is a higher incidence of academic difficulties in children with cystinosis compared with the general population. Although any area of academic study may be challenging to some children with cystinosis, the most common area of difficulty is with arithmetic. In one study, 37% of children with cystinosis scored below normal levels on tests of arithmetic and spelling (Ballantyne et al., 1997). Although fewer children demonstrated difficulty with reading, 20% had reading scores below the normal mean. These data have been corroborated by independent information from the CCIR, in which 37% of school age individuals with cystinosis reported problems with math, and 26% of 183 respondents reported reading difficulties.

There are several possible causes for learning issues in children with cystinosis. Having a chronic illness may make the child feel fatigued and make it more difficult to concentrate. Many of the medications that must be taken on a daily basis may cause nausea, headaches and other symptoms that make the child feel too ill to complete school work. There are other unrelated learning disabilities that can co-occur with any chronic disease. However, the visual spatial problems associated with cystinosis may contribute to learning problems as well. Arithmetic in particular requires good spatial awareness to master. For example, when doing addition, we need to know where to start (on the right side), where to go next to carry numbers (up and to the left), and where to write the numbers in the answer. Similarly, subtraction, multiplication and other arithmetic functions require a good deal of spatial awareness in order to get the answers correct (See Figure 4, right, for an example). Thus, children who have visual spatial difficulty might be more likely to experience academic difficulties as well. Fortunately, for those children there are interventions that may improve their academic performance.

D. OTHER COGNITIVE ISSUES

Some children with cystinosis exhibit problems with paying attention or staying focused. At times there may be problems in the area of executive functioning. Executive functioning is a complex set of functions that include higher-level cognitive processes such as initiation (e.g., of a conversation, an idea, or a motor act), planning, problem-solving, cognitive flexibility, behavioral regulation, and utilization of feedback from others or from outside information such as reading a textbook. Executive functions are extremely important in order for an individual to develop into an independent, socially successful person. A small percentage of individuals with cystinosis have greater than usual difficulty in the areas of switching attention, cognitive flexibility, and reasoning. These deficits may make it more challenging for them to develop full independence or to successfully obtain and maintain employment.
E. NON-VERBAL LEARNING DISABILITY (NVLD) IN CYSTINOSIS

Non-verbal learning disability (NVLD or NLD) is a condition in which individuals have a specific set of strengths and deficiencies that may result in academic difficulties. The characteristic features of NVLD include normal intelligence, good language and reading skills, but deficits in mathematics, handwriting, visual spatial processing, visual motor performance, and nonverbal problem solving. Children with NVLD may also have associated problems with attention, and social difficulties. Many of the children with cystinosis have a similar pattern of strengths and weaknesses, and for some of these children a diagnosis of NVLD may be appropriate, and can help teachers and resource specialists to understand the needs of some cystinosis children who may be struggling academically.

F. POTENTIAL CAUSES FOR COGNITIVE DYSFUNCTION IN CYSTINOSIS

At this time it is not known why some individuals with cystinosis have cognitive differences. We do know that these problems are present early in life, at least by age 3, in some children, and that a substantial percentage may experience academic difficulties during school years. There are several potential causes for the observed cognitive issues. In cystinosis, cystine begins to accumulate in the body early in life, most likely even before birth. It is possible that early cystine accumulation in the brain causes a difference in the way the brain develops. We have studied the development of white matter in the brain in children with cystinosis (Bava et al., 2010) and looked at how differences in white matter development correlated with visual spatial function. The white matter in the brain is made up of nerve cell fibers that connect one nerve cell to another throughout the brain. These fiber networks are responsible for different parts of the brain communicating with one another. If the white matter is not fully functional, this may result in incomplete communication among brain cells, and
this in turn may cause slower processing of information going into the brain. In addition, certain areas of the brain (the parietal lobes) are thought to be responsible for visual spatial functions while different parts of the brain (the temporal lobes) are thought to be responsible for visual perception without a spatial component.

In our study of brain structure and function in cystinosis, we used a technique called diffusion tensor imaging to analyze the integrity of white matter in the parietal lobes of 24 children with cystinosis. We found that there was a delay in maturation of the white matter specifically in the parietal lobes of children with cystinosis when compared with healthy children of the same age. This delay in maturation was seen at the ages of 3 through 7 years. By close to 8 years of age, brain white matter integrity appeared to have “caught up” with that of age-matched controls. However, visual spatial function was still impaired in the cystinosis group. We interpreted these results to indicate that there is an early delay in the maturation of certain parts of the brain responsible for visual spatial function, and that although the brain structurally appears to catch up to expected levels by age 8, the delay in maturation results in a perhaps permanent impairment in visual spatial function in these children.
Given the cognitive and academic difficulties that some children with cystinosis experience, as well as the problems associated with coping with a chronic illness, the possibility of behavioral issues is important to consider. We studied behavioral profiles of children with cystinosis using a behavioral checklist (the Achenbach Behavior Checklist) that was administered to parents of 64 children with cystinosis. We also obtained questionnaires from parents of 21 children with another chronic illness, cystic fibrosis (CF), to determine whether any behavior problems might be related to having a chronic illness as opposed to being specific to cystinosis. A control group of 101 healthy children was also included. The results of the study indicated that children with cystinosis had a significantly higher incidence of social problems compared with CF or controls, and that the cystinosis group had a much higher rate of attention problems, thought problems, and aggression than would be expected compared with the general pediatric population.

Social problems stood out as being the major problem area for children with cystinosis compared with the CF group. Most of the social issues were related to acting younger than their chronological age, being excessively “clingy” with adults, and choosing to play with children younger than they are.

Another study of behavior in cystinosis utilized a parent questionnaire developed in our laboratory. Over one third of the 63 parents indicated that their child’s behavior was more intense than that of other non-affected children. 65% of parents reported that their child had temper tantrums or severe mood swings. Tantrums were not limited to toddlers; 54% of parents whose children were 8 years of age or older reported persistent temper tantrums. Parents also reported a high incidence of defiance, irritability, being overly-dependent (not self-reliant), and being overly sensitive (getting their feelings hurt easily). Additional issues noted by a high percentage of parents included their child’s poor problem-solving abilities, difficulty recognizing limitations, impulsiveness, and demanding that others do things for him/her rather than doing things on their own.

A recently completed study from our laboratory of adolescents with cystinosis compared with another disease control group, Type I diabetes, showed similar findings as the earlier studies: teens with cystinosis were more likely to have social difficulties and to be less independent than their peers. Figure 5 shows the results of questionnaire data that demonstrates that adolescents with cystinosis have lower scores
on measures related to quality of life both at school and also as relates to their views of their health, compared with healthy adolescents and with adolescents with diabetes mellitus.

It appears, then, that both children and adolescents with cystinosis are at higher risk for certain types of behavioral and adjustment issues than either healthy peers or peers with other chronic disease. Awareness of this possibility can lead to early intervention with counseling or psychotherapy when indicated, and help to reduce the problems and prevent longterm difficulties.

---

**Figure 5.** Mean scores on quality of life measures for healthy adolescents, age-matched teens with Type I diabetes, and teens with cystinosis. Scores were significantly lower for both attitudes towards general health and also quality of life related to school in the cystinosis group compared with the other 2 groups.

**Quality of Life Measures**

- QQL Health
- QQL Health

---

**Legend:**

- Ctrl
- JDM
- Cyst
A very rare late complication of cystinosis has been called cystinosis encephalopathy. This condition has been reported in a very small number of adults with cystinosis. It consists of a deterioration in cognitive and motor function, with slowing of speech, memory loss and confusion, as well as tremor and loss of ability to walk. The cause of the encephalopathy has not been identified, but Broyer et al. (1996) reported that treatment of 4 adults with cysteamine appeared to stabilize and reverse some of the symptoms in 3 of the 4. Fortunately, the condition is very rare, and at this time it is not clear whether individuals treated with cysteamine are at risk for developing this complication.
Another late complication of cystinosis is a progressive muscle weakness that occurs in young adults. The weakness and muscle wasting, or atrophy, typically begins in the hands, and then progresses to involve the muscles of the mouth and face, shoulder and arm muscles. In severe cases it may involve the muscles of the chest as well (Charnas et al., 1994). Figure 6 shows a microscopic picture of muscle tissue from a young adult with cystinosis, showing an abnormal muscle fiber that is typical of a myopathic process. The muscle weakness is slowly progressive over the course of years. The cause of the muscle wasting is not well defined as yet. It is possible that cysteamine may slow the progression of the weakness, but it is not clear that this treatment prevents the muscle problems from developing. Our studies of cystinosis myopathy suggest the possibility that there is a problem with energy production in the muscle due to mitochondrial dysfunction. The mitochondria are small structures within the cells that produce energy. If they are not working properly, there is reduced energy available to the cells and this can cause weakness in the muscles. Whether this is the only cause of the myopathy is not clear and requires further study.

Figure 6. Abnormal ring muscle fiber in the muscle tissue of a young adult with cystinosis.
Fortunately, there are interventions that can help individuals with cystinosis who have neurological, cognitive, and/or academic difficulties. The most important factor is to identify the problem. If a child appears to be having challenges with learning, for example, then neuropsychological testing should be considered to identify the underlying cognitive differences that might account for the learning difficulty, such as a visual spatial problem. If a child is unusually clumsy or has difficulty with fine motor skills such as cutting with a scissors or tracing or coloring within the lines, a neurological or occupational therapy consultation should be considered. Once the underlying issue is identified, a rational approach to intervention can be planned.

Fine motor incoordination can often be helped through an occupational therapy program that uses a systematic approach to improving fine motor skills. Gross motor problems such as extreme clumsiness or inability to throw or kick a ball may be helped through a physical therapy program, or adaptive physical education programs through the school may be a good alternative.

Behavioral issues are not uncommon in children with cystinosis, as mentioned above. Many of these may be expected merely from the multitude of blood tests, doctors’ visits, and medications that these children must endure. However, even though the behaviors can be rationalized by their illness, if the behaviors become disruptive to home or school life or if they impair social interactions with peers, consideration should be given to behavioral therapy with a clinical child psychologist. In particular, a play-based therapeutic program such as Floortime may be useful in working with even very young children to improve behavior. Behavior modification plans can also be developed with the aid of a psychologist. These can be used both at school and at home to help the child to develop more control of his/her behaviors and learn more appropriate ways of dealing with frustration.

Teenagers with cystinosis may experience social difficulties and find it hard to develop independence. Medication adherence may be a major problem at this stage of development as well. Refusing to take medications can result in kidney failure, and so it is crucial that these issues be dealt with promptly. Counseling and psychotherapy may be of benefit in these situations. Teens should also be encouraged to develop independence in terms of taking responsibility for their medications, learning about their medical condition, and taking on other age-appropriate responsibilities such as chores, after-school jobs, and extra-curricular activities.

As mentioned above, seizures may occur with higher frequency in individuals with cystinosis. If a person has more than one unprovoked seizure, an anticonvulsant medication is usually needed to prevent future seizures and the complications associated with them. There are many anti-seizure medications available. Many of the newer medications
do not cause cognitive side effects and do not have a risk of causing kidney damage. If a person with cystinosis has seizures, it is important to discuss with the physician which medication is least likely to worsen the cystinosis-related medical issues.

Interventions for cognitive and learning issues are also available. It is important to first determine what the primary cognitive issue is. If the child has visual spatial deficits and academic difficulties related to this, a number of types of interventions may be considered. Occupational therapy and/or vision therapy (performed usually by a developmental optometrist) aimed at improving visual spatial skills may help the underlying deficit. At school, several strategies can help to improve the child’s academic functioning.

Since the primary problem is often a visual spatial difficulty, the use of verbal strategies can help the child to learn. Verbal strategies include using verbal descriptions of the academic material, describing steps verbally as well as demonstrating visually, and in general talking through a problem such as a math problem rather than just showing the work on a chalkboard or monitor. For written work such as math tests, simplifying the visual input can help. For example, if the test includes 20 arithmetic questions and they are all printed out on a single page, this presents a complicated picture for a person with a visual spatial problem. It is difficult to concentrate on which problem to work on, how to go from one to the next, and so on. By reducing the number of math problems on the page, or allowing the child to cover up all but the one s/he is working on, this can reduce the spatial confusion and help the child to focus on one math problem at a time. Finally, reducing the amount of work or allowing the child an increased amount of time to complete assignments can be very helpful.

Math is not the only area of academic function that may be problematic for children with cystinosis. If a child is struggling in school, it is important to have the child tested to determine what the underlying deficit is so that intervention can be appropriately focused. Many children with cystinosis take longer to process visual information than do their peers. Providing additional time to complete the work will allow them the time they need to process the information and to be more successful academically.

Some examples of ways to help children with academic challenges include the following. Not all are necessary or even appropriate for every child, but the teacher and the parent may be able to identify specific techniques that can best help the individual student.

- Sequence materials and activities from simple to complex.
- Allow additional time to complete assignments and tests.
- Reduce the amount of visual information presented on a page.
- Suggest mnemonic devices to help with memorizing facts. Singing the alphabet is a mnemonic device. “Every good boy does fine” is a mnemonic that children learn when they first study music to remember the lines of the treble clef (EGBDF). Mnemonic devices are very effective in aiding memory.
- Use examples, illustrations, tables, pictures, audio tapes and videos to aid learning.
- Highlight key words or concepts by writing them on the chalkboard or showing them on a projector, leaving the words visible long enough for the child to rehearse and/or copy them.
- Provide handouts with key words or new information at the beginning of class.
- Try to use concrete examples to help explain abstract concepts.
- Allow the student to use a computer for written assignments.
- Allow the student to record lectures so that s/he can listen to them later in order to more effectively remember what was taught.
CONCLUSIONS

Cystinosis is a multi-system disorder. The nervous system is prominently involved in this condition (although not in every person with cystinosis). Coordination, balance, strength, behavior, cognitive and academic functioning may be areas of difficulty for some children and adults with cystinosis. Muscle problems may also be a prominent feature of nephropathic cystinosis. Recognition that these problems can occur in cystinosis can lead to early diagnosis and more effective treatment interventions for many of the neurological complications of cystinosis.


Cure Cystinosis International Registry March 2012.


