Visual and verbal learning and memory in cystinosis

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ABSTRACT

Cystinosis is a rare genetic lysosomal storage disorder characterized by the accumulation of cystine in lysosomes. Many organ systems are vulnerable to this cystine accumulation including the CNS. A past study demonstrated that children with cystinosis have deficits in visual learning and memory while their verbal learning and memory and global intellectual function are spared (Spilkin, Ballantyne, & Trauner, 2009). However, no related study has been performed to assess the dissociation between visual and verbal learning and memory in adults with cystinosis who have had the benefit of longterm treatment with the cystine-depleting agent, cysteamine. In this study we assessed visual and verbal learning and memory in 15 adults with cystinosis, with a mean age of 30.2 years. The results indicate that adults with cystinosis have no significant deficits in either verbal or visual learning and memory. However, the individuals did perform better on the verbal assessment. The results suggest that if early and continued treatment is given to individuals with cystinosis there is a relative sparing of visual learning and memory that might have otherwise declined. This emphasizes the essential nature of the proper clinical management of cystinosis.

1. Introduction

Cystinosis is a rare autosomal recessive metabolic disorder affecting lysosomal function. As with most lysosomal storage disorders, multi-organ dysfunction is common, although the kidney is the first to be severely affected. Until the advent of successful renal transplantation, the disease was often fatal in the first decade of life. The availability of a cystine-depleting agent (cysteamine) has also significantly improved longevity, and currently people with cystinosis are living well into adult life and with fewer and less severe systemic complications. As life expectancy increased, the awareness of central nervous system involvement in this condition also increased. Children with cystinosis were found to have a specific cognitive deficit, visual spatial dysfunction, on a background of normal intelligence and preserved language functions (Ballantyne et al., 1997; Ballantyne and Trauner, 2000; Elmonem et al., 2016; Kensinger, 2009; Nichols et al., 1990; Trauner et al., 2007; Trauner et al., 1988). This deficit was found to be present, although to a milder degree, in carriers of the gene, who are otherwise asymptomatic but demonstrate visual spatial deficits relative to other areas of cognitive functioning (Niemiec et al., 2012). A detailed study of visual and verbal learning in children with cystinosis (Spilkin, Ballantyne, & Trauner, 2009) identified a dissociation between the two domains, while visual learning was impaired relative to controls. This study also found that adults with cystinosis performed more poorly in both visual and verbal learning than did children with the disorder, suggesting a progressive detrimental effect of the disease on cognitive functioning. Following up on the cognitive dissociations, Bava et al., conducted a study of microstructural changes in the brains of children with cystinosis using diffusion tensor imaging (DTI) techniques. The investigators demonstrated structural changes in the brain that appear to correlate with the cognitive findings. Specifically, Bava et al., 2010 found that children with cystinosis between the ages of 3 and 7 years had reduced white matter integrity as evidenced by fractional anisotropy (FA) in parietal lobules with intact FA in temporal lobes compared with age-matched controls. Moreover, FA correlated directly with performance on a visual spatial task, suggesting that early structural changes in parietal lobes during development might negatively impact cognitive outcome in cystinosis.

Since the above studies were completed, advances in both the diagnosis and treatment of cystinosis have continued. With more awareness of the condition by practitioners, children are being diagnosed earlier. Similarly, the approval of cysteamine by regulatory bodies in many countries has made the availability of this treatment fairly widespread, and currently children are beginning treatment very early in life. Cysteamine was approved by the United States Food and
Drug Administration for the treatment of nephropathic cystinosis in 1994. Thus, individuals with cystinosis born since that time have had access to early treatment, and are now well into adult life. Many have improved general health and are without major medical complications in many cases. It is not known, however, whether this improvement in general health extends to cognitive functioning.

The current study was designed to determine whether adults with cystinosis who have been well treated with cystine-depleting agents from childhood, continue to exhibit differences in visual and verbal learning, or whether early treatment has a modulatory effect on the previously observed cognitive dissociations.

2. Methods

2.1. Participants

The cystinosis group consisted of 15 adults with cystinosis, 8 males and 7 females, with a mean age of 30.2 years old (age range 25–38 years old; standard deviation 4.41). All were diagnosed because of typical clinical features and elevated leukocyte cystine levels. The participants were recruited from advertisements placed on various cystinosis foundation websites, as well as from the Cystinosis Research Foundation Day of Hope family conference. Demographic information was obtained from all participants, including age at diagnosis, age at which treatment was begun, transplant status and related information. The subjects were excluded from the study if they had a glomerular filtration rate lower than 60 mL/min or any other medical condition that could contribute to memory deficits. They were also excluded if they had been previously tested with the VLMT or CVLT. Informed consent was obtained in accordance with UCSD’s Institutional Review Board processes.

The control subjects used were from a previously acquired normative database collected by Spilkin et al. (2009). The adult controls from that normative database were used as an adult control group in this study. All controls were healthy adults with IQ in the normal range, no history of medical problems, and age range between 20 and 40 years. Details of these participants are found in Spilkin et al. (2009).

2.2. Measures

Wechsler abbreviated scale of intelligence: The Wechsler Abbreviated Scale of Intelligence (WASI) is a measure of global cognitive functioning (Wechsler, 1999). There are 4 subtests: Matrix Reasoning, Block Design, Vocabulary, and Similarities, each with a mean T score of 50. The subtests are combined to compute 3 overall IQ scores: Performance IQ, Verbal IQ, and Full Scale IQ. The composite IQ scores have a mean of 100 and a standard deviation of 15.

Visual learning and memory test: The Visual Learning and Memory Test (VLMT) is a test of visual learning and memory developed in Dr. Trauner’s laboratory and was created as a visual analog to the California Verbal Learning Test (CVLT). In this task, the subject is shown 15 abstract designs, one design per second, and then is presented with a grid of 30 abstract designs (15 are the designs presented, and 15 are foils). The participant is then asked to mark which 15 designs were presented. This is repeated for five trials. The order in which the designs are presented is always the same, but the locations of the designs on the grid are randomized. After the fifth trial, a 20-min recess is taken from the task while the participant completes other testing. A sixth, delayed recall trial is then completed and the participant is asked to indicate which 15 designs they were shown in the previous five trials.

Raw scores from this test do not account for both correctly picked designs and incorrectly chosen foils. Thus, in order to properly evaluate a participant’s score, a d’ value was calculated, which accounts for both correct designs that were chosen as well as the incorrect foils that were chosen by the participant.

The mean d’ score represents an individual’s performance over the course of the five learning trials and is the best measure of overall visual learning on the VLMT, since it takes into account both accuracy and false “hits” (report of a stimulus that was not actually given during the test). The individual d’ scores for each of the learning trials and of the delayed recall trial were computed as well. Trial 1 d’ represents immediate visual memory. Trial 5 d’ represents overall learning performance. Trial 6 d’ represents visual long-term memory (Spilkin et al., 2009).

California verbal learning test: The California Verbal Learning Test (CVLT) is a standardized test of verbal learning and memory (Delis, Kramer, Kaplan, & Ober, 2000). In this task, the participant is read 16 words, one word per second, and then asked to recall as many words as possible. This same list is presented for five trials, and after each trial the participant is asked to recall as many words as the participant can. A distractor list is then presented, and immediately following the participant is asked to recall as many words from the first list as possible. Lastly after a 20-min recess, the participant is asked to recall as many words as possible from the first list. The total number of words remembered over the five learning trials is used as an indication of overall verbal learning ability. The number of words recalled after trial one assess short term verbal memory, and the number of words recalled after a 20 min delay assess verbal long term memory. Raw and standard T-scores are calculated by a CVLT computerized scoring system.

3. Results

3.1. Demographic information

All of the adults with cystinosis were diagnosed before 2 years of age and begun on appropriate treatments for their Fanconi syndrome and other metabolic abnormalities. Ten of the 15 adults with cystinosis were begun on cysteamine by 2 years of age. Two additional participants began treatment at ages 4 and 5 years old, and 2 reported never having taken this medication.

3.2. Wechsler Abbreviated Scale of Intelligence

All individuals with cystinosis had intelligence scores within the normal range (Table 1).

3.3. Visual learning and memory

A repeated measures analysis of variance (ANOVA) was run comparing d’ on the VLMT between the control group and the cystinosis group. The within-subject variable was trial 1–5 and the between subjects variable was group. There was a significant effect of trial

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There was not a significant effect of group \( (F_{1,45} = 1.408, p > 0.05) \) or trial × group \( (F_{3.547,159.630} = 1.585, p > 0.05) \). See Fig. 1 for learning curves. A repeated-measures ANOVA was used to assess how well each group retained the presented information after a 20-min delay. The difference between trial 5 and the 20 min delay, was the within subject variable and the group was the between subject variable. There was not a significant effect of trial \( (F_{1,45} = 0.5, p > 0.05) \), group \( (F_{1,45} = 3.613, p > 0.05) \) or trial × group \( (F_{1,45} = 0.255, p > 0.05) \). See Fig. 2 for retention of information after a delay.

3.4. Verbal learning and memory

A repeated measures ANOVA was run comparing the performance on trial 1–5 between the control group and the cystinosis adults. The trial was the within subject variable, and the group was the between subjects variable. There was a significant effect of trial \( (F_{3.547,159.630} = 61.148, p < 0.0005) \). There was not a significant effect of group \( (F_{1,45} = 1.408, p > 0.05) \) or trial × group \( (F_{3.547,159.630} = 1.585, p > 0.05) \). See Fig. 1 for learning curves. A repeated-measures ANOVA was used to assess how well each group retained the presented information after a 20-min delay. The difference between trial 5 and the 20 min delay, was the within subject variable and the group was the between subject variable. There was not a significant effect of trial \( (F_{1,45} = 0.5, p > 0.05) \), group \( (F_{1,45} = 3.613, p > 0.05) \) or trial × group \( (F_{1,45} = 0.255, p > 0.05) \). See Fig. 2 for retention of information after a delay.

3.5. Visual versus verbal asymmetry analysis

An asymmetry analysis was run to determine if either the cystinosis or control group did significantly better on either the CVLT or the VLMT. The best measure of overall learning on the VLMT is the value mean d’ trials 1–5. On the CVLT, the best measure of overall learning is mean number of words recalled over trials 1–5. First, both scores were converted to T scores so the two tests could be compared. For the analysis, the T score from the CVLT was subtracted from the T score from the VLMT. A score of 0 would indicate an individual did equally well on the VLMT and CVLT, while a positive value indicates an individual did better on the VLMT than the CVLT. A negative score indicates an individual did better on the CVLT than the VLMT. See Fig. 5 for the T score differences for the control and cystinosis groups. Results indicate that the cystinosis group did better on the verbal learning task, whereas the controls did slightly better on the visual learning task but with a very small T-score difference.
4. Discussion

The results from this study suggest that adults with cystinosis who have received consistent treatment of their underlying disease have normal visual and verbal learning and memory. However, consistent with previous studies, they performed better on the verbal learning and memory assessment than on the visual learning and memory assessment.

The adults with cystinosis performed as well as the controls on trial 1 on the CVLT and VLMT suggesting normal verbal and visual short-term memory. They also performed as well as controls on the measure mean trial 1–5, suggesting normal overall global visual and verbal learning. Trial 6 scores were not significantly different between the control and cystinosis groups, indicating normal visual and verbal long-term memory. Taken together these results indicate that adults with cystinosis who have received consistent treatment with a cystine-depleting agent since early life have normal visual and verbal learning and memory. In contrast, Spilkin et al. (2009) past study demonstrated an overall decline in functioning on the VLMT and the CVLT as individuals with cystinosis aged. However, the adults with cystinosis in this current study performed equivalently to an age matched control group and there was no indication of a decline. A major change in the recognition and treatment of cystinosis is likely the cause for the differences in the findings between the two studies. There is better awareness and earlier recognition of the disease, associated with earlier treatment with a cystine-depleting medication that has been shown to maintain renal function and delay renal failure and the need for transplantation for many years. Other advances in treatment have also resulted in overall better health and longevity in people with cystinosis. This improvement in the overall clinical management of cystinosis may also be beneficial in terms of preventing or reducing cognitive deficits such as visual learning and memory challenges as individuals with cystinosis age. This emphasizes the importance of early and ongoing treatment of this disease. It also suggests that, with optimal treatment, cognitive functioning and memory do not necessarily decline with age in cystinosis.

Nevertheless, a dissociation between visual and verbal learning was still present, with visual learning somewhat lower than verbal learning (Fig. 5). This may relate to structural changes in the brain demonstrated in a previous study (Bava et al., 2010) that found a lag in parietal white matter development in children with cystinosis compared with age-matched controls. Since the parietal lobe is involved in visual perceptual processes, early differences in brain development in this region could lead to long-term differences in visual learning.

There were some limitations in this study that need to be addressed. The statistical power of this study was limited by the small sample size, as cystinosis is a rare condition. However, this limitation was partially alleviated since only individuals who were well enough to travel and therefore, in overall general good health were included in this study. This makes for a rather homogenous group of adults with cystinosis, who are in good general health, have good renal functioning, and can work and travel independently. This fact may limit the generalizability of the results, since individuals with poor renal functioning were not included. A further limitation was that a specifically demographic and aged matched control group was not used. However, the previously developed normative database used to standardize the VLMT utilized in this study was extensive.

In conclusion, the results of this study indicate that cognitive functioning and memory in adults with cystinosis, who are in otherwise good health, does not necessarily decline with age. This is an important finding because it suggests that with early and consistent management of this disease, a potential decline in cognitive functioning can be prevented.

Declaration of Competing Interest

None.

Acknowledgements

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2019.103578.

References