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## CEREBROVASCULAR COMPLICATIONS OF L-ASPARAGINASE THERAPY IN CHILDREN WITH LEUKEMIA: Aphasia and Other Neuropsychological Deficits

**A. Kingma, MSc, R. Y. J. Tamminga, MD, PhD, and W. A. Kamps, MD, PhD**

□ Division of Pediatric Oncology, University Hospital of Groningen, The Netherlands

**R. Le Coultre, MD** □ Division of Pediatric Neurology, University Hospital of Groningen, The Netherlands

**R. J. Saan, MSc** □ Division of Neuropsychology, University Hospital of Groningen, The Netherlands

□ *Children with acute lymphoblastic leukemia (ALL), treated with L-asparaginase are at risk for cerebral thrombosis or hemorrhage because of coagulation protein deficiencies. The results and the importance of serial neuropsychological examinations after such complications in three children with ALL are presented. All patients showed marked aphasia and other cognitive deficits. Recovery was complete in two of three children.*

**KEY WORDS:** *aphasia in children, cerebrovascular accident, L-asparaginase, acute lymphoblastic leukemia, neuropsychological deficits.*

### INTRODUCTION

L-asparaginase (ASP) is a major component of remission induction therapy in children with acute lymphoblastic leukemia (ALL). ASP therapy results in asparaginase depletion and therefore in deficiencies of important coagulation proteins which may lead to hemorrhage or thrombosis in the central nervous system (CNS). This unwanted effect of ASP occurs in about 1%–2% of the patients, usually 3–4 weeks after the beginning of ASP therapy. Hematological and neurological findings associated with this complication have been well described.<sup>1–5</sup> Residual neurological sequelae of cerebral thrombosis or hemorrhage following ASP therapy in children with ALL have also been reported. In a review of 34 patients, it was concluded that, although 22 of the surviving 27 children completely recovered, detailed neuropsychological examinations might have revealed possible cognitive impairment.<sup>6</sup>

We report here neuropsychological findings in the only three children with ALL who had clear cerebrovascular accidents (CVA) associated with ASP in our institution (with 20 newly diagnosed leukemia patients per year) over the past 10 years. In these patients, neuropsychological deficits including aphasia and behavioral disturbances were among the most impressive symptoms. Assessment of neuropsychological functions was most important in determining course, recovery and later quality of life in these patients.

## PATIENTS AND METHODS

At diagnosis, our patients were aged 10, 12, and 16 years, respectively. Day of onset of the CVA, in relation to induction treatment, ASP administration, and coagulation profiles are shown in Table 1. After their CVA, patients were treated with fresh frozen plasma, cryoglobulin and platelets. Patients also received temporary anticonvulsive treatment, either phenytoin or carbamazepine.

**TABLE 1.** Treatment, Including L-Asparaginase Administration and Coagulation Profile in Three Patients with Acute Lymphoblastic Leukemia Suffering a CVA

Treatment before CVA	ASP adm.		CVA; Days from Dx	Coagulation parameters at CVA		
	Days	Schedule		Fibrinogen (g/l)	AT III (%)	Platelet count ( $\times 10^9/l$ )
1 L-asparaginase dexamethasone vincristine it methotrexate	11	6000 U/m <sup>2</sup> iv daily	35	0,84	61	?
2 L-asparaginase daunorubicin dexamethasone vincristine 6 mercaptopurine it methotrexate prednisone cranial irradiation <sup>1</sup>	32	25000 U/m <sup>2</sup> im weekly	61	0,70	66	172
3 L-asparaginase daunorubicin it methotrexate prednisone	14	10000 U/m <sup>2</sup> iv every 3 days	47	0,41	74	74

CVA, cerebrovascular accident; ASP, L-asparaginase; adm., administration; Dx, diagnosis; it, intrathecal; im, intramuscular; iv, intravenous.

<sup>1</sup>24 Gy cranial irradiation in patient with meningeal leukemia at diagnosis.

A first neuropsychological assessment (NPA) was possible within 10 days after the CVA and repeated several times thereafter, depending on the clinical course and recovery. Follow-up was 24 months. NPA included measures of intelligence,<sup>7</sup> attention, short- and long-term verbal memory, visual-motor integration, tactile perception, fine motor functioning and assessment of right-left orientation and body image. Aphasia screening was mainly done with the Dutch SAN test, which includes several measures of productive and comprehensive language. All tests that were used in the aphasia examination are summarized in Table 2.<sup>8-13</sup> All children received psychological counseling, language stimulation, and other rehabilitation measures. Parents and health-care professionals were informed about the cognitive disabilities and received instructions on how to communicate with the patient.

**CASE REPORTS; NEUROPSYCHOLOGICAL COURSE**

**Patient 1**

A 10-year-old, right-handed girl had a hemorrhagic infarction of the left temporal lobe, resulting in a right-sided hemiparesis, hemianopsia, and generalized seizures. A first NPA could be performed 10 days after the CVA.

Spontaneous language was limited to five words, and communication was maintained by gesticulation. Sounds, letters, and words could not be repeated. She could not name objects nor read aloud. The productivity score of the SAN test was below the fourth percentile if compared to normative data. She could use her dominant right hand but could only write simple and automatized words such as her own name. Although less striking, there certainly were difficulties with comprehension of words

**TABLE 2.** Aphasia Examination in Three Children with Acute Lymphoblastic Leukemia Suffering a CVA after L-Asparaginase Administration

Test	Measurements of
SAN (Dutch Aphasia Test)	Spontaneous language
	Sound discrimination
	Sentence production
	Word fluency } Productivity score
	Object naming } Productivity score
Tokentest 5th series	Sentence comprehension } Receptivity score
	Word comprehension } Receptivity score
	Receptive language
Fluency test (naming as many animals as possible in 1 minute)	Verbal fluency

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and sentences; the receptivity score of the SAN test also was below the fourth percentile, and she could not perform a single task of the Token test. There was right-left confusion and distortion of body image. Visual-spatial and constructive functions were unaffected. We noted apraxia, but there was an interference with the receptive language disorder. Emotionally, she reacted adequately and showed normal intelligence in her nonverbal behavior. We diagnosed a predominantly nonfluent aphasia together with a receptive disorder and a possible apraxia as a result of a left temporal lobe lesion.

### Course

There was a fast, day-to-day recovery of all language (related) functions. Receptive difficulties were the first to disappear. The fluency test, naming as many animals as possible within 1 minute, showed a gradual improvement from naming 2 animals after 1 week to a score of 12 animals after 4 weeks. Five months after the CVA, no more aphasic symptoms were found with normal performance on the productivity and receptivity scales of the SAN test. Intelligence and memory testing yielded age-appropriate scores, although the girl complained of little impairment in memory, fluency, and academic performance. She was doing well at school but had to repeat her grade 2 years later, while she used to be among the best in her class before she became ill. Leukemia treatment, omitting the ASP infusions, was stopped 27 months after diagnosis. At that time all motor functions were normal; the only residual neurological sequelae were a slightly diminished sense of temperature in the right hand and minor problems in her previous gymnastic class.

### Patient 2

A 12-year-old, right-handed girl had multiple infarctions in both cerebral hemispheres ( $R > L$ ) resulting in a left-sided hemiplegia, hemianopsia and seizures. A first NPA could be performed 8 days after the CVA.

Spontaneous speech was sparse, slow and limited to concrete remarks or overlearned phrases; "yes" and "no" were used improperly. Word fluency and repeating sentences were below age level. Receptivity score of the SAN test was within normal age limits but the productivity score was on the sixth percentile. She could read but with too many mistakes. Writing and visual-perceptual functions were unimpaired. We could not diagnose a complete nonfluent aphasia, but expressive language functions were affected, possibly as part of the general bradyphrenia.

### Course

NPA 2 months after the CVA showed major improvement, including normal use of language and an excellent score on the fluency test. Verbal memory and intelligence seemed to correspond with the estimated pre-morbid level. Neurological examination showed a very mild residual right hemipareses. Six months later, 1 year after the CVA, she was readmitted with a long-lasting left partial seizure with secondary generalization and postictal lowered consciousness for some days. Another NPA showed marked cognitive impairment, including a nonfluent aphasia with a productivity score below the fourth percentile on the SAN test. One month later, language functions were improved and well enough for school reentry. However, her parents worried about her negative behavior and poor relationships with peers. By 2 years after the CVA, a last NPA showed no aphasic symptoms, although her score on the fluency test never became as good as before. Right-hand finger tapping, verbal-auditory memory and intelligence were still impaired (WISC-R IQ 80) and she had to repeat grades. Her former personality had slightly changed. Neurologically, only nystagmus and an absent Achilles tendon reflex were left. Leukemia treatment without the last three doses of ASP was stopped 5 months earlier than scheduled because of the serious complications.

### Patient 3

A 16-year-old, right-handed boy had a left parieto-occipital hemorrhage with intraventricular extension, resulting in a right-sided hemiplegia and seizures. Initial NPA was spread out over 2 weeks because of his poor clinical condition.

At first the patient was very anxious, with fluctuating consciousness and hardly any communication; sometimes he could nod "yes" or "no." After some days he could say a few words and three-word sentences. One week after the CVA his productive score on the SAN test was below the fourth percentile, and we diagnosed a nonfluent aphasia. Spontaneous speech was repetitive and word fluency was grossly impaired (naming one animal in 1 minute). He could read aloud but not without errors. There was left-sided finger agnosia, right/left confusion and distortion of body image. Memory, especially for new and recent information, was impaired, and he often asked the same questions. Perceptual functions of this previously very bright boy appeared unaffected. Receptive language was slightly impaired. Two weeks after the CVA, expressive language was clearly improved, but reading speed was still slow for his age and word fluency very poor (naming three animals). Writing with his left nondominant hand, fingergnosis, body image and left-right orientation were

normal again. Right-hand paresis interfered with the examination of stereognosis but he couldn't recognize objects at all with his right hand. Verbal memory span was unaffected, but storage of new verbal information was very poor.

### Course

Three months after the CVA, memory and fluency testing showed appropriate scores for his age, although the boy himself still complained about his poor memory and impaired fluency. Aphasic symptoms were absent. Results of a third NPA 6 months later showed a superior intelligence (IQ 134) and a still better excellent verbal memory. All language (related) functions were normal, and his spontaneous language was quick and bright. Two years after the CVA there are no complaints about any cognitive function. He is doing very well in school. Motor functioning has greatly improved but is still not up to standard with a slight right-sided hemisyndrome. ALL treatment was finished according to protocol.

### DISCUSSION

In our patients, overall recovery and neuropsychological outcome was good in two of the three cases. However, serious impairment of speech and other cognitive functions were found in all of them in the first weeks to months after the CVA. Our patients suffered from language disorders consistent with left hemisphere damage. Such lesions in adults would probably result in persistent serious damage to speech. The impressive language defects of our patients markedly improved but it is not necessarily so that children always recover from acquired aphasia.<sup>14,15</sup> The bilateral damage in one of our patients could account for her poorer outcome, including impairment of intelligence and emotional functions. It is remarkable that impaired cognitive functions were hardly mentioned in reports on cerebrovascular complications of ASP therapy.<sup>6</sup> Neuropsychological symptoms are easily missed or underrated and may impede proper treatment and counseling of patients. We strongly recommend neuropsychological examination if previously mastered (language) skills are lost in association with ASP therapy. If no (neuro)psychologist or speech pathologist is available, recording of speech and short tests such as picture/object naming, word fluency, repeating words and sentences, writing and reading can be investigated by a physician or nurse. Recording of deficits is important because (1) change in behavior of the patient can be explained and hence, parents and hospital staff can be advised with regard to the communication with the child; (2) recovery can be monitored as neurological recovery is not always accompanied by

recovery of cognitive functions; and (3) school re-entry can be determined and educational services can be guided. Problems in school could be among the most persistent sequelae and, if not recognized, can be the cause of much frustration in the child later on.<sup>16</sup>

We conclude that besides neurological and imaging examinations, repeated neuropsychological assessment has an important contribution in determining further medical and psychological management of a pediatric patient with cerebrovascular complications following treatment for leukemia, including ASP.

## REFERENCES

1. Feinberg WM, Swenson MR. Cerebrovascular complications of L-asparaginase therapy. *Neurol.* 1988;38:127-133.
2. Priest JR, Ramsay NKC, Latchaw RE, et al. Thrombotic and hemorrhage strokes complicating early therapy for childhood acute lymphoblastic leukemia. *Cancer.* 1980;46:1548-1554.
3. Priest JR, Ramsay NKC, Steinherz PG, et al. A syndrome of thrombosis and hemorrhage complication L-asparaginase therapy for childhood acute lymphoblastic leukemia. *J Pediatr.* 1982; 6:984-989.
4. Priest JR, Ramsay NKC, Bennett AJ, Krivit W, Edison JR. The effect of L-asparaginase on antithrombin, plasminogen, and plasma coagulation during therapy for acute lymphoblastic leukemia. *J Pediatr.* 1982;6:990-995.
5. Pui CH, Jackson CW, Chesney C, et al. Sequential changes in platelet function and coagulation in leukemic children treated with L-asparaginase, prednisone, and vincristine. *J Clin Oncol.* 1983;6:380-385.
6. Ott N, Ramsay NKC, Priest JR, Lipton M, Pui CH. Sequelae of thrombotic or hemorrhagic complications following L-asparaginase therapy for childhood lymphoblastic leukemia. *Am J Pediatr Hematol Oncol.* 1988;10:191-195.
7. Wechsler D. *Wechsler Intelligence Scale for Children—Revised.* New York: The Psychological Cooperation; 1974.
8. Deelman BG, Koning-Haanstra M, Liebrand WBG, van den Burg W. *SAN Test, Handleiding.* Lisse, The Netherlands: Swets en Zeitlinger; 1981.
9. Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders.* Philadelphia, PA: Lea & Febiger; 1972.
10. Luteyn F, van der Ploeg FAE. *GIT, Handleiding.* Lisse, The Netherlands: Swets & Zeitlinger; 1983.
11. van Harskamp F, van Dongen HR. Construction and validation of different short forms of the Tokentest. *Neuropsychologica.* 1977;15:467-470.
12. Halperin JM, Zeitchik E, Healy JM, Weinstein JM, Ludman WL. The development of linguistic and mnemonic abilities in normal children. *J Clin Exp Neuropsychol.* 1989;11:518-528.
13. Lezak MD. *Neuropsychological Assessment.* New York: Oxford University Press, 1983.
14. van Dongen HR. *Clinical Aspects of Acquired Aphasia and Dysarthria in Childhood.* Rotterdam, The Netherlands: Erasmus University, 1988. Dissertation.
15. van Hout A. Acquired aphasias in children. In: Segalowitz SJ, Rapin I (Eds). *Handbook of Neuropsychology*, section 10: Child Neuropsychology. Amsterdam, London, New York, Toronto: Elsevier; 1992.
16. Cranberg LD, Filley CM, Hart EJ, Alexander MP. Acquired aphasia in childhood: Clinical and CT investigations. *Neurol.* 1987;37:1165-1172.

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Address correspondence to A. Kingma, Department of Pediatrics, University Hospital of Groningen, 59, Oostersingel, 9713 EZ Groningen, The Netherlands.