Long-term neuropsychologic outcome in children diagnosed with low-grade astrocytoma

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Neuropsychologische gevolgen bij kinderen,
die gediagnosticeerd zijn met een laaggradig astrocytoom

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. Dr. H.G. Smidt

en volgens het besluit van het College voor Promoties.

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door

Femke Kirina Aarsen
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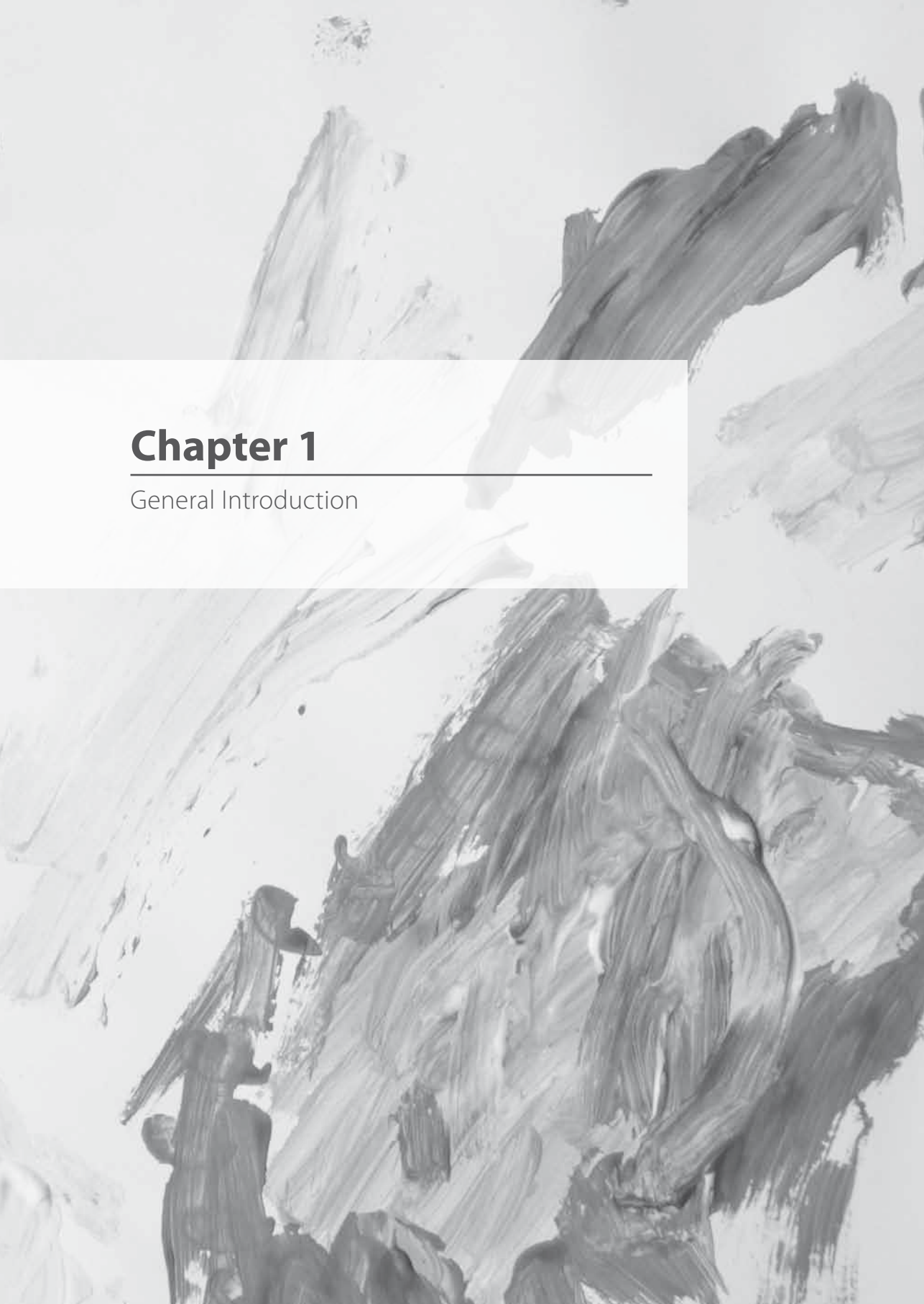
Toen Freud de divan bedacht,
plagieerde hij de biechtstoel.
Katholieken wisten al eeuwen dat het helpt,
het eens aan iemand te vertellen.
Maar psychiaters kunnen geen vergiffenis schenken.
Daarom duren de analyses zo kostbaar lang.

Simon Carmiggelt

Aan mijn ouders, Rutger, Silvijn, Marie-Lise en Sweder

CONTENTS



Chapter 1

General Introduction

INTRODUCTION

Central nervous system (CNS) tumors in children have a relatively high frequency. They are the second most common form of cancer in childhood only exceeded by acute lymphoblastic leukemia (ALL). However, prognosis is more severe and at present more children die because of CNS tumor than of ALL. The incidence of CNS tumors is estimated 3.5 per 100,000 in children below 15 years of age.[1] Boys appear to be at greater risk than girls (1.1:1) and this ratio is even higher in primitive neuro-ectodermal tumor (PNET), plexus papilloma, and germinoma (2:1).[1] The most frequently occurring histological tumor type is astrocytoma (40-50%) followed by medulloblastoma (15-20%), ependymoma (8-13%), and craniopharyngiomas (7-10%) as shown in Table 1.[2] Astrocytomas are classified according to increasing malignancy grade as pilocytic, fibrillary, anaplastic astrocytoma, and glioblastoma. The most common variant in children is the pilocytic astrocytoma.

Symptoms of CNS tumors may arise from indirect effects caused by increased intracranial pressure (ICP) interfering with brain functions or direct local effect of the tumor by compression or destruction of normal neural tissue. Children with low-grade astrocytoma (LGA) often present with symptoms and signs due to raised ICP: headache, vomiting, lethargy, visual

Table 1 Classification of CNS tumors (modified to the new WHO Classification of Brain tumors)[2]

Tumors of neuro-epithelial tissues
1. Astrocytic tumors
2. Oligodendroglial tumors
3. Mixed gliomas
4. Ependymal tumors
5. Choroid plexus tumors
6. Glial tumors of uncertain origin
7. Neuronal and mixed neuronal-glial tumors
8. Neuroblastic tumors
9. Pineal parenchymal tumors
10. Embryonal tumors
Tumors of peripheral cranial and paraspinal nerves
1. Schwannoma
2. Neurofibroma
3. Perineurinoma
4. Malignant peripheral nerve sheath tumor
Tumors of the meninges
1. Tumors of meningothelial cells
2. Mesenchymal, non-meningothelial tumors
3. Primary melanocytic lesions
4. Tumors of uncertain histogenenis
Lymphomas and haemopoietic neoplasms
Germ cell tumors
Tumors of the sellar region
Metastases

problems, papilledema, macrocephaly or behavioral changes.[3] Because these symptoms are not specific, diagnosis may be delayed for a long period. Direct local effects cause neurologic impairments depending on the localization and size of the tumor. They may include ataxia, visual impairments, eye movement disorders, pyramidal signs, seizures, hearing loss, and facial palsy.[4] In case of a hypothalamic localization, endocrine dysfunctions may occur such as growth hormone deficiency, hypogonadotrophic hypogonadism, hypothyroidism, precocious puberty, hypoadrenalism, and diabetes insipidus in various combinations and degree of severity.[5,6]

First choice of treatment of a brain tumor is neurosurgical total resection.[2] If a total resection is not within the realms of possibility, biopsy or (partial) resection at least yields a histological diagnosis. The extent of the resection is in many tumor types an important prognostic factor.[2] Adjuvant treatment depends on extent of the resection, site, histologic type, and grading of the tumor.[7] Neurologic impairments after tumor resection can lead to moderate or severe invalidating disabilities.[8] Treatment of intracranial tumors with radiation therapy may result in long-term side effects such as radio necrosis, myelopathy, leukoencephalopathy, endocrine deficiencies, vascular injury, bone and tooth abnormalities, ocular complications, ototoxity, induction of second primary tumors, baldness, and neurocognitive problems.[9] The diffuse white matter changes can lead to intellectual deficits resulting in difficulties acquiring new knowledge, decreased processing speed, and short-term memory deficits.[9] Younger age, larger fields, and higher doses appear to result in a higher rate of neurocognitive deficits.[10] Neurologic complications of chemotherapy with methotrexate or Ara C can lead to leukoencephalopathy.[11]

Low-grade brain tumor

LGA include pilocytic and fibrillary astrocytoma and may occur everywhere in the central nervous system. Preferred localizations are visual pathways, (hypo) thalamus, and cerebellum.[2] First choice of treatment for LGA is total resection. However, localization in functionally crucial structures often is a contra-indication of radical surgery such as the optic nerve or chiasma glioma or intrinsic tumor of the (hypo)thalamus. Adjuvant chemotherapy, radiotherapy or both are indicated in case of tumor growth or relapse.[3] The 5-year survival rate is 80 to 90% and depends on tumor site and extent of resection.[2] The relatively high survival rate necessitates increasing attention to physical and psychosocial outcome. In spite of the benign histology and the favorable survival rate of LGA, functional outcome seems affected but firm conclusions as to the pattern or frequency of neurologic or neuropsychologic impairments, disabilities, handicaps, and Quality Of Life (QOL) cannot be drawn from the available studies.

Long-term neuropsychologic outcome in children with acquired brain injury

Long-term effects of acquired brain injury (ABI) can be classified into the three global domains of cognitive, behavioral and social-emotional functioning.[12-15] There can be a great heterogeneity of combinations and severity of possible cognitive, behavioral or social-emotional consequences. This depends on the site and size of the lesion, age of onset, or the traumatic or non-traumatic origin of the lesion.[15] Late neurocognitive consequences may consist of problems with attention, speed, novelty learning, executive functioning, and language.[12] For example, 20% of children with severe traumatic brain injury have a diagnosis of secondary attention deficit with hyperactivity disorder (s-ADHD).[13] In children with posttraumatic ABI there are more problems with mathematics and reading comprehension than with spelling or technical reading.[15] Problems with social-emotional functioning include emotional instability or diminished social problem solving skills.[14] Behavioral impairments include aggressive behavior, anger, impulsivity, anxiety, diminished self-control, diminished initiation, and inappropriate behavior.[15]

Cognitive functioning in children diagnosed with LGA

Studies on cognitive deficits in small series of children with LGA show intellectual deterioration, memory, attention, and executive problems.[4,6,16-25] Neuropsychologic assessment in larger series has not systematically been done in children with LGA. Studies on cognitive deficits in children shortly after treatment of cerebellar Pilocytic Astrocytoma (PA) describe problems with affect regulation, memory, attention, language, speech, visual-spatial, and executive functions.[16,17] Follow-up studies of long-term sequelae after cerebellar PA surgery have included tests of intellectual functioning but not a systematic assessment of other functions.[4,17-21] They report the following long-term cognitive impairments: attention deficits in seven children,[19] executive problems in three out of four children,[20] difficulties with reading, spelling and working memory in one patient, [21] language, visual-spatial or memory difficulties in three patients.[17]

Three studies describe long-term cognitive deficits after treatment of PA in the cerebral hemisphere.[4,22,23] In the study of Yule[4] two children had a subnormal IQ of 87 one year after resection of a cerebral hemisphere PA. After resection of temporal lobe astrocytomas five out of seven children had intellectual deterioration, learning disabilities or psychopathology.[22] In a study of 14 children after resection of temporal lobe tumors, the majority had an increased risk for memory dysfunction, and academic failure three years after treatment.[23]

The conclusions of three studies on cognitive sequelae after treatment of a supratentorial midline PA are ambiguous. [6,24,25] In one study, children with optic pathway tumors had normal intelligence, memory, and fluency three years after chemotherapy with the exception of children with neurofibromatosis type 1 (NF1) and children who received radiotherapy.[24] Irradiated children scored lower for abstract reasoning, arithmetic, coding, perception, and

judgment of line orientation.[24] Children with NF1 showed subnormal IQ scores with short- and long-term memory problems.[24] In two other studies of children with hypothalamic or chiasmatic tumor, intelligence was significantly compromised at diagnosis,[6] and remained below average after six years.[6] They frequently required special education after three years.[25]

Low-grade tumors of the tectal plate typically occur in children.[3] At this site total resection is rarely possible and because of the indolent nature of this tumor also rarely necessary. Children often present symptoms or signs of raised ICP due to obstruction of the aqueduct and treatment is limited to alleviation of hydrocephalus.[3] Reports in children with tectal plate tumor have been limited to observed cognitive deficits after treatment and reported observations are attention deficits, learning disabilities, and memory deficits. [26-28] Formal assessments of neuropsychologic functioning have not been performed in children with tectal plate tumor after treatment for obstructive hydrocephalus.

Behavioral and emotional problems in children diagnosed with LGA.

In the first days after resection of a cerebellar tumor, a neurobehavioral syndrome of sub acute onset, named the Posterior Fossa Syndrome (PFS) may occur.[29] The PFS is a childhood syndrome with largely transient symptoms and signs. Symptoms develop one to six days postoperatively and gradually resolve after a period varying from days to months. The most common feature is mutism; this is often referred to as Mutism and Subsequent Dysarthria (MSD) syndrome and mostly occurs in children with medulloblastoma.[30] Other features of MSD syndrome are oropharyngeal dyspraxia, emotional lability, incontinence and bizarre personality changes.

In contrast to the detailed descriptions of cognitive and behavioral problems in the acute postoperative phase such as PFS/MSD syndrome, reports of long-term behavioral impairments after cerebellar PA surgery are still scarce: persisting behavioral difficulties in one patient[17], and passive, immature and childish behavior in another patient.[16] Parents describe demoralization, increased sensitivity and lower frustration tolerance. They experience the behavioral problems as more disabling than the concomitant cognitive impairments.[20] In other localizations of LGA, reports of long-term behavioral effects are very limited and are only described in a small series. After treatment for temporal lobe astrocytomas five out of seven children were reported to have psychiatric problems.[22] The majority of 14 children with temporal lobe tumors had an increased risk for internalized or externalized behavior problems three years after treatment.[23]

QOL in children with LGA.

The psychosocial consequences of a brain tumor have exclusively been described in adult survivors of childhood brain cancer in general.[23] These adults had higher levels of global dis-

tress, lower household income, lower educational attainment, and were frequently unmarried and unemployed. The QOL in adult survivors of childhood brain cancer is significantly lower in the domains of depression and somatization.[23] Just one study specifically evaluates QOL in survivors of childhood cerebellar PA. Medical doctors simply regard the QOL in this group as "cured and fare well".[25] However, scores on a QOL questionnaire are significantly lower on all scales except for sex life. The scales cognition, well-being, memory, socializing, and adolescence measured the most severe deficits.[25]

OBJECTIVES OF THE PRESENT STUDY

Children with a diagnosis of LGA have a relatively high survival rate and their QOL is usually seen as "fares well".[31] They attend school and will participate in professional work. However, how they "fare" at long-term in real life is largely unknown. A wide variety of problems is described in small series: neurologic impairments, cognitive deficits, behavioral and emotional dysfunction and a lower QOL. This necessitates increasing attention to physical, cognitive and psychosocial outcome.

The general objective of the work described in this thesis is first to investigate the long-term neuropsychologic outcome of children with a diagnosis of LGA in order to detect deficits that may require timely intervention. This information is important for the design of intervention programs that could ameliorate QOL and participation in society. The second objective is to identify possible risk factors such as age, interval diagnosis-assessment, tumor characteristics, hydrocephalus, relapse, treatment characteristics, and postoperative status. Insight in risk factors may lead to treatment strategies to prevent neuronal damage which negatively interferes with the neuropsychologic outcome.

PATIENTS AND METHODS

Patients

Between 1993 and 2004 a consecutive series of 83 children was treated for LGA at Erasmus MC/Sophia Children's hospital. Two children were included who had a histological diagnosis of another type of low-grade brain tumor (neurocytoma, ganglioglioma). They were included in studies 2, 3, 4, and 5. The general inclusion criteria for these studies were age at surgery ≤ 18 years, interval surgery to assessment ≥ one year. Children with NF1 were excluded because of their specific cluster of deviant behavioral and cognitive impairments.[32] Between 1987-2007, all children in a consecutive series of 148 children treated for a cerebellar tumor were included in study 6. Informed consent was not necessary, because all data were col-

lected with assessments according to the standard clinical follow-up protocol of the Society for pediatric oncology in the Netherlands (SKION).

Methods

Level of functioning was systematically assessed according to the levels described by the WHO standards at the time of inclusion which are: *disease process*, *impairment* (the general effect of the disease on the child), *disability* (the restriction of the ability to perform tasks within the physical and social environment), *handicap* (the social consequence of these impairments and disabilities in the domains of relationships, school, leisure activities), and *QOL* (the sense of the child's well-being and life satisfaction in physical, social, and emotional domains). [33]

Disease process

Pre- and postoperative brain MRI's were studied to determine preoperative maximum tumor diameter, site of the tumor, incision site, postoperative lesion diameter, and ventricle dilatation at presentation and at assessment. We computed the bicaudate index (BI) as a measure of ventricle dilatation at presentation.[34] In children included in the study described in chapter 2 perfusion of different brain areas was visualized semi quantitatively by means of postoperative 99mTc-hexamethylpropyleneamine oxime-Single Photon Emission Computed Tomography (SPECT) scans.

Impairments

Children were examined to establish residual neurologic impairments. Speech was assessed according to the "Mayo Clinic Lists"[35], in which speech characteristics such as voice quality, nasality, articulation, prosody and respiration are included.[36] Blood tests were done to detect growth hormone deficiency, thyroid hormone deficiency, adrenal insufficiency, pubertas praecox, and diabetes insipidus.

Disabilities

Disabilities were expressed in the pediatric modified Rankin scale[37] or in percentages of children needing remedial teaching or special education. The degree of the disability was divided into three categories:

1. No motor or learning disabilities (Rankin scale 0). Patient attends regular school.
2. Mild motor disturbances, mild learning disability or both (Rankin scale 1 or 2). Patient is able to attend regular school, but needs remedial teaching.
3. Severe motor disturbances, severe learning disability or both (Rankin scale 3-5). The child attends a school for special education or a day care center.

Table 2 Neuropsychologic assessment in children diagnosed with low-grade brain tumor

	Psychologic tests/questionnaires	Study 1	Study 2	Study 3	Study 4	Study 5
Intelligence	Wechsler Intelligence Scales	X		X		
	Raven (Colored) Progressive Matrices				X	
Attention	Stroop Color-Word test	X		X	X	
	Cancellation-test	X		X	X	
Memory	Rey CFT	X		X	X	
	RAVLT	X		X	X	
Executive skills	TMT	X		X	X	
	Verbal fluency	X		X	X	
	W (M) CST	X		X	X	
Visual-spatial skills	Beery VMI	X		X		
	Rey CFT	X		X	X	
	JLOT				X	
	FRT				X	
	Line Bisection				X	
Language/Speech	Token test/TROG	X		X	X	
	BNT	X		X		
	Mayo Clinic list			X	X	X
Behavior	CBCL		X	X		
	YSR		X	X		
	TRF		X	X		
QOL	TACQOL-C		X			
	TACQOL-P		X			

Handicaps

Handicaps were evaluated with a behavior checklist for parents (Child Behavior Checklist; CBCL), for children older than eleven years (Youth-Self Report; YSR) and for teachers (Teacher Record Form; TRF). [38] The scales of the general part of the behavior checklist are activities, relationships and school. The scales of the specific behavioral part are withdrawal, somatic complaints, anxious/depressive, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. Information on the presence of learning disabilities and on actual school situation was obtained from parents and teachers. Behavioral disturbances were also evaluated from an observation of the child and interviews with the parents according to DSM IV criteria.[39]

(Neuro)psychologic tests (Table 2) developed for children and young adults were administered to assess skills in six domains: intelligence, memory, language, visual- (spatial) functions, executive skills, and attention. [40-51] All tests were administered in their Dutch versions. Manifest neuropsychologic deficits, spontaneous language and speech were judged by clinical appraisal.

Quality of life

Quality of life (QOL) was assessed with TNO/AZL Children's Quality of Life questionnaires (TACQOL).[52] There is a parent form (TACQOL-P) and a form for children older than eight years (TACQOL-C). Measured scales are physical, motor, autonomy, cognition, social functioning, positive and negative emotions.

Statistics

The performances of the patients on the tests and questionnaires were compared with the normative data and converted into Z scores. The Z score reflects the extent a score deviates from the mean of a normal population. The χ^2 test was used to compare variance of our study group with the normal population and the Kolmogorov-Smirnov test was used to control for normal distribution. Differences between two or more groups were analyzed with the Mann-Whitney *U* test, the Kruskall-Wallis test, and Spearman rank correlations. Data that fulfilled the requirements of parametric testing and had $n \geq 20$ were analyzed with two-sided Students t test, ANOVA, univariate, and multivariate analysis with Bonferonni corrections. A two-sided Pearson correlation matrix was computed. In a normal population 2.3% of children have Z-scores ≤ -2. We considered it of clinical importance when the percentage of children in our study obtained a Z-score exceeding 2.3%. Backward stepwise linear regression based on highest partial correlations obtained in a Pearson correlation matrix, was used to identify parameters that predict significantly lower scores on the neuropsychologic tests in the entire PA group. Included risk factors were sex, age at diagnosis, age at assessment, interval diagnosis-assessment, relapse, kind of treatment, size and site of tumor/lesion, BI at diagnosis, BI at assessment, and presence of ventriculoperitoneal (VP)-drain or ventriculostomy. Maximum number of predictors was set on three because of the sample size. Univariate and multivariate analysis was performed after regression analysis

Outline of this thesis

In Chapter 2 cognitive functioning, QOL, educational results and their predictors are investigated three years after diagnosis in a large consecutive pediatric series treated for LGA in different parts of the brain. In chapter 3 long-term functional outcome in children diagnosed with LGA is examined in the domains of impairments, disabilities, handicaps, and QOL. Chapter 4 focuses on neurologic and neuropsychologic deficits in children with low-grade tectal tumors to study the effect of acquired obstructive hydrocephalus on cognitive functioning. This was done to study the role of hydrocephalus in the development of late cognitive dysfunction in more detail because hydrocephalus at tumor presentation was found to be an important risk factor for neuropsychologic dysfunctions in children with LGA in chapter 2. In Chapter 5 long-term neurologic and cognitive sequelae in children treated for a cerebellar PA are examined. In addition, risk factors and results of education were evaluated. In chapter 6 behavioral sequelae in children treated for a cerebellar tumor are described and a possible

risk factor for neurocognitive dysfunctions such as PFS is examined. Finally in Chapter 7 the main findings and conclusions of this thesis are discussed and implications for medical practice are given.

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Chapter 2

Cognitive deficits and predictors three years after diagnosis of a pilocytic astrocytoma in childhood.

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ABSTRACT

Objective

To prospectively study cognitive deficits and predictors three years after diagnosis in a large series of pediatric patients treated for pilocytic astrocytoma (PA).

Methods

Sixty-one of 67 children were grouped according to infra-, supra- midline, and supratentorial hemispheric site. Intelligence, memory, attention, language, visual-spatial and executive functions were assessed. Included predictors were sex, age, relapse, diagnosis-assessment interval, hydrocephalus, kind of treatment, and tumor variables.

Results

All children with PA have problems with sustained attention and speed. In the infratentorial group there also were deficits in verbal intelligence, visual-spatial memory, executive functioning, and naming. Verbal intelligence and verbal memory problems occured in the brainstem tumor group. The supratentorial hemispheric tumor group had additional problems with selective attention and executive functioning and the supratentorial midline tumor group displays no extra impairments. Specifically the dorsal supratentorial midline tumor group displayed problems with language and verbal memory. Predictors for lower cognitive functioning were hydrocephalus, radiotherapy, residual tumor size, and age; predictors for better functioning were chemotherapy or treatment of hydrocephalus. Almost 60% of children had problems with academic achievement, for which risk factors were relapse and younger age at diagnosis.

Conclusion

Despite normal intelligence at long-term follow-up, children treated for PA display invalidating cognitive impairments. Adequate treatment of hydrocephalus is important for a more favorable long-term cognitive outcome. Even children without initial severe deficits may develop cognitive impairments years after diagnosis, partly because of the phenomenon "growing into deficit" which has devastating implications for academic achievement and quality of life (QOL).

INTRODUCTION

Astrocytomas account for approximately one third of pediatric central nervous system (CNS) tumors.[1] They are classified according to increasing malignancy grade as pilocytic, fibrillary, and anaplastic astrocytoma. The first-choice treatment for PA is complete surgical resection. Adjuvant chemotherapy or radiotherapy is reserved for recurrent or progressive, inoperable disease. The long-term survival for children with PA is approximately 90% after four years, whereas survival for patients in individual series of cerebellar PA with gross total resection may be 90 to100%.[2]

Long-term studies on cognitive deficits in children after treatment of cerebellar PA describe problems with affect regulation, memory, attention, language, speech, visual-spatial, and executive functions in different combinations and to different degrees.[3,4,5] These deficits fit in the spectrum of the cerebellar cognitive affective syndrome (CCAS).[6]

Three studies describe long-term cognitive deficits after treatment of PA in the cerebral hemisphere.[7-9] In the study of Yule et al., two children with cerebral hemisphere PA had a subnormal IQ of 87 at one year after treatment.[7] After treatment for temporal lobe astrocytomas, five out of seven children were reported to have intellectual deterioration, learning disabilities, or psychopathology.[8] The majority of 14 children with temporal lobe tumors had an increased risk for memory dysfunction, academic failure, and internalized or externalized behavior problems three years after treatment.[9]

Conclusions in three studies on cognitive sequelae of treatment of a supratentorial midline PA are ambiguous. In one study, children with optic pathway tumors had normal intelligence, memory, and fluency three years after chemotherapy with the exception of children who had neurofibromatosis type 1 (NF1) and children who received radiotherapy.[10] In two other studies of children with hypothalamic and chiasmatic tumor, intelligence was significantly compromised at diagnosis,[11] remained below average after six years[11] and frequently required special education for the children after three years.[12]

Long-term cognitive deficits contribute to impairments, that have an impact on functional outcome such as school achievement and Quality of Life (QOL). In a consecutive series of 38 children with low-grade astrocytoma, functional outcome was significantly decreased in all domains of the QOL questionnaire except for emotions.[13] Predictors for a worse functional outcome were surgical damage, [3-5,14] hydrocephalus at diagnosis,[3] radiotherapy, [7] age[13] or relapse.[13]

The purpose of the present study was to prospectively assess cognitive deficits and predictors three years after diagnosis in a large consecutive pediatric series treated for pilocytic astrocytoma in different parts of the brain.

PATIENTS AND METHODS

Patients

Between 1994 and 2004, a consecutive series of 67 children without NF1 were treated for PA at Erasmus MC/Sophia Children's hospital. Children with NF1 were excluded because of their specific cluster of deviant behavioral and cognitive impairments.[15] Sixty-one patients (28 boys) could be tested according to our standard clinical follow-up protocol. Two patients with diencephalic tumors died six and 12 months, respectively, after diagnosis and one patient refused neuropsychologic assessment. Three children were lost to follow-up. Eighteen children and their parents filled in a QOL questionnaire at the time of assessment. Results were described in an earlier study.[13]

Methods

All children had a standardized pediatric neuro-oncologic follow-up every six months and a standardized neuropsychologic assessment at six months, 18 to 24 months, and 3 to 4 years after diagnosis in a multidisciplinary outpatient clinic. The data of the last assessment were used and the interval between two assessments was at least 21 months.

Preoperative MRI or CT scans with and without contrast enhancement were reviewed for ventricle width, presence of VP shunt, ventriculocisternostomy, and the preoperative size and site of the tumor. Postoperative MRI scans at time of assessment were used to determine the ventricle width, resection site, VP shunt, and presence or size of residual tumor at time of neuropsychologic assessment. According to tumor site three groups were defined: an infratentorial (brainstem and cerebellum), a supratentorial hemispheric, and a supratentorial midline group (ventral and dorsal). The ventral group comprised children with a tumor in the chiasm or adjacent hypothalamus and the dorsal group consisted of children with a tumor in the thalamus, the basal ganglia or both. The group left-sided tumors included left-sided supratentorial hemispheric, left-sided midline and because of the crossed connections between the cerebral hemispheres and the contra lateral cerebellum right-sided infratentorial tumors. The group right-sided tumors included right-sided supratentorial hemispheric, right-sided midline, and left-sided infratentorial tumors. We computed the bicaudate index (BI) as a measure of ventricular dilatation at presentation and at time of assessment.[3] We distinguished: no (BI < 0.19), mild (BI 0.19-0.26), and severe hydrocephalus (BI > 0.26). A pediatric

neurologist (C.C-B.) examined all children to establish residual neurologic impairments and to determine academic achievement at time of neuropsychologic assessment.

The neuropsychologic assessment included intellectual functioning with the age-appropriate Dutch version of the Wechsler Scales (WPPSI-R or WISC-R), [16] memory, [17,19,20,21] attention, [17,21] language, [17,22,23] visual-spatial[17,18,20,21] and executive skills[17,20,21] (see table 2). Quality of life was assessed with the parent form of TNO/AZL Children's Quality of Life questionnaires for children aged six to 15 years (TACQOL-PF)[24] and the children's form for children aged eight to 15 years (TACQOL-CF).[24]

Statistics

The data of the neuropsychologic assessment were compared with the normative data of the Dutch population and were corrected for age. To compare the performances of all children all scores were converted into Z-scores. The χ^2 test was used to compare variance of this study group with the normal population. The Kolmogorov-Smirnov test was used to control for normal distribution. Data were analyzed with the Mann-Whitney *U* test, Kruskal-Wallis test, and Spearman rank correlations. Data that fulfilled the requirements of parametric testing and had $n \geq 20$ were analyzed with two-sided Students t test, ANOVA, univariate, and multivariate analysis with Bonferonni corrections. A two-sided Pearson correlation matrix was computed. In a normal population 2.3% of children have Z-scores ≤ -2. We considered it of clinical importance when the percentage of children in this study obtained a Z-score exceeding 2.3%. Backward stepwise linear regression based on highest partial correlations obtained in a Pearson correlation matrix, was used to identify parameters that predict significant lower scores on the neuropsychologic tests in the entire PA group. Included risk factors were sex, age at diagnosis or assessment, diagnosis-assessment interval, relapse, kind of treatment, size and site of tumor/lesion, BI at diagnosis or assessment, and presence of VP drain. Maximum number of predictors was set on three because of the sample size. Univariate and multivariate analysis were performed after regression analysis (SPSS 16.0).

RESULTS

Neurologic data

Median age at diagnosis was seven years and eight months (interquartile range 3.2 – 11.4 years) and median age at assessment was 11 years and three months (interquartile range 8.9 – 15.1 years). The median follow-up period was three years and six months (interquartile range 2.0 – 5.0 years). In all children neuropathologic diagnosis was confirmed by means of biopsy (n = 9) or (partial) resection (n = 52). Fifteen of 61 children needed other therapy: chemotherapy (n = 11) and stereotactic radiotherapy (n = 4) (see Figure 1). Sixteen children

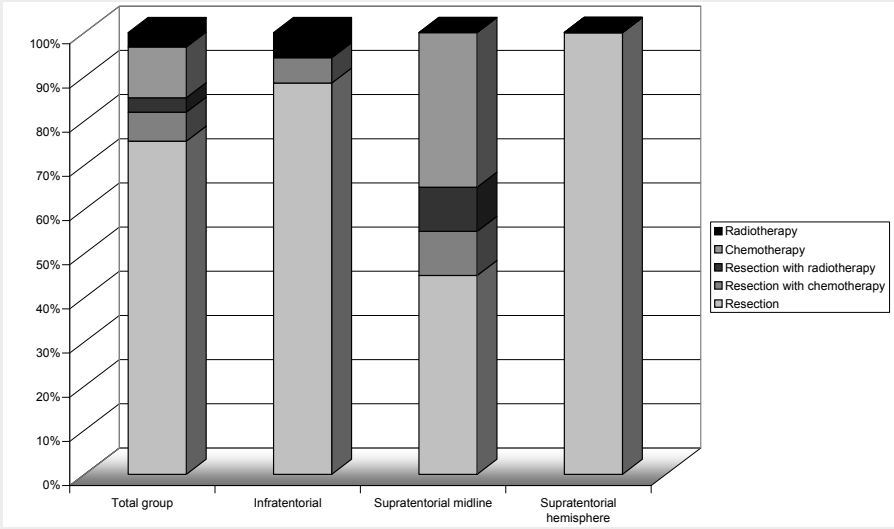

Figure 1 Treatment characteristics after initial diagnosis

had one or more relapses and its treatment consisted of re-resection (n = 11), (adjuvant) chemotherapy (n = 9), or (adjuvant) radiotherapy (n = 10). The chemotherapy scheme consisted of vincristine and carboplatin according to the International Society of Pediatric Oncology - Low Grade Glioma (SIOP-LGG) protocol.

Table 1 shows the patient characteristics and the neurologic impairments at time of assessment. Thirty-five children had an infratentorial tumor (brain stem: 6, cerebellum: 29). Out of 26 children with supratentorial tumors six had a hemispheric tumor and 20 had a midline tumor (ventral: 10, dorsal: 10). Thirty-four children had no, 11 mild, and 16 had severe hydrocephalus at first presentation. In five children VP shunt was inserted before and in 18 after tumor resection. One child was treated with ventriculocisternostomy. At time of assessment five children still had a mild hydrocephalus.

Education and QOL

Education results showed that 59% of the children needed special education services (21% special education, 38% received remedial teaching (RT) by a specialized Dutch institution on a normal school). These children had significant lower scores on tests measuring sustained attention (Cancellation test-fluctuations, $p = 0.02$), speed (Cancellation test-speed, $p = 0.02$), long-term memory (Rey CFT-delayed recall, $p = 0.01$, RAVLT delayed recall, $p = 0.02$), executive functioning (TMT B, $p = 0.02$) and QOL (TACQOL-CF domain Motor, $p = 0.03$; domain Cognition, $p = 0.04$ and TACQOL-PF domain Cognition, $p = 0.01$, domain Autonomy, $p = 0.05$) than

Table 1 Clinical patient characteristics

	Total Group (n = 61)	Infratentorial (n = 35)	Supratentorial hemisphere (n = 6)	Supratentorial midline (n = 20)
Max diameter tumor (cm)	4.60 ± 1.57	5.00 ± 1.29	5.80 ± 2.30	3.60 ± 1.22
Max diameter residue (cm)	1.25 ± 1.55	0.62 ± 0.90	2.10 ± 2.20	2.80 ± 0.09
Left/right-sided tumor	14/15	6/7	2/4	6/4
Post-operative BI	0.11 ± 0.05	0.10 ± 0.05	0.11 ± 0.03	0.12 ± 0.05
Pre-operative shunting	8%	9%	0%	10%
Peri-operative shunting	30%	23%	0%	50%
1st Relapse	26%	20%	33%	35%
2nd Relapse	8%	9%	0%	10%
3rd Relapse	2%	0%	0% (0)	5%
Education – normal	41%	37%	17%	55%
Education – normal and RT	38%	43%	50%	25%
Education – special	21%	20%	33%	20%
Motor problems	56%	69%	33%	40%
Epilepsy	5%	0%	17%	10%
Visual disorder	15%	9%	0%	30%
Visual field defect	28%	6%	17%	70%
Somatic sensory deficit	0%	0%	0%	0%
Auditory sensory deficit	0%	0%	0%	0%
Hormone deficiency	15%	3%	0%	40%

Notes
Max = maximum, cm = centimeter, BI = Bicaudate Index, RT = Remedial Teaching

children without RT or special education. Neurologic independent factors influencing type of education were relapse or a younger age at diagnosis.

Neuropsychologic data

Six children (three with a cerebellar, three with a supratentorial midline PA) were under the age of six at time of assessment. They were too young to perform the tests measuring language, attention, memory, executive, and visual-spatial skills with exception of verbal fluency and the Beery VMI. In comparison with the normal population (see Table 2) the entire PA group showed weaker performances on tests measuring sustained attention (Cancellation test-fluctuations, $p < 0.001$), speed (Cancellation test-speed, $p < 0.001$), executive functioning (TMT A and B, $p< 0.001$; WCST: perseverations, $p <0.001$), naming (BNT, $p<0.02$), and long-term visual-spatial memory (Rey CFT-delayed recall, $p < 0.001$). Forty-four percent of children showed a discrepancy between performance (TPIQ) and verbal intelligence (TVIQ). This is significantly more than in the normal population ($p < 0.001$). In 56% of children TVIQ was lower than TPIQ.

Factors influencing cognitive outcome

Regression analysis was performed on the significantly weaker performances of these tests , and it showed that there were no significant predictors for impairments of speed (Cancella-

Table 2 Neuropsychologic outcome in IQ and Z scores (mean ± SD) for total, infratentorial, supratentorial midline, and supratentorial hemispheric group

	Neuropsychologic tests	Total (n = 61)	Infratentorial (n = 35)	Supratentorial hemispheric (n=6)	Supratentorial midline (n=20)
Intelligence	FSIQ	99 ± 16	97 ± 16	103 ± 17	100 ± 17
	TVIQ	95 ± 17	**91 ± 14***	101 ± 20	96 ± 19
	TPIQ	101 ± 17	102 ± 18	106 ± 16	99 ± 18
Attention	Stroop Color-Word test°	0.56 ± 2.41	-0.20 ± 2.75	**-2.44 ± 1.46***	-0.48 ± 1.84
	Cancellation-test-speed°	**-2.00 ± 2.92****	**-2.38 ± 3.05****	**-2.31 ± 3.79***	**-1.21 ± 1.05****
	Cancellation-test fluctuations°	**-2.38 ± 1.51****	**-2.17 ± 1.21****	**-3.55 ± 2.19***	**-2.37 ± 1.68****
Memory	Rey CFT- delayed recall°	**-0.69 ± 1.02****	**-0.81 ± 0.98****	-0.75 ± 0.80	-0.45 ± 1.16
	RAVLT 1-5°	-0.16 ± 1.41	-0.35 ± 1.40	0.82 ± 1.23	-0.14 ± 1.40
	RAVLT delayed recall°	-0.09 ± 1.25	-0.18 ± 1.19	0.20 ± 1.13	-0.01 ± 1.43
Executive skills	TMT A°	**-0.85 ± 1.30****	**-1.16 ± 1.45****	-0.56 ± 0.82	-0.33 ± 0.92
	TMT B°	**-0.77 ± 1.47****	**-0.92 ± 1.52****	-1.34 ± 1.57	-0.32 ± 1.31
	Verbal fluency	0.29 ± 1.36	0.17 ± 1.30	0.13 ± 1.17	0.56 ± 1.55
	WCST perseverations°	**-0.75 ± 0.47****	**-0.76 ± 0.37****	-0.60 ± 1.05	-0.73 ± 0.78
Visual-spatial skills	Beery VMI	-0.14 ± 1.02	-0.23 ± 1.13	0.60 ± 1.02	-0.31 ± 0.80
	Rey CFT- copy°	0.14 ± 1.03	-0.09 ± 1.05	0.62 ± 0.66	0.42 ± 1.02
Language	Token test°	0.10 ± 0.94	0.18 ± 0.80	1.65 ± 1.05	-0.27 ± 1.19
	BNT°	**-0.60 ± 1.36***	**-1.02 ± 1.36****	0.34 ± 2.66	-0.22 ± 1.11

Notes °
total group (n = 55), infratentorial (n = 32), supratentorial hemispheric (n=6), supratentorial midline (n = 17), ** = p<0.01 in comparison to normative data, * = p<0.05 in comparison to normative data, FSIQ = total intelligence, TVIQ = total verbal intelligence, TPIQ = total performance IQ, Rey CFT-delayed recall = delayed recall version of Rey Complex Figure Test, RAVLT = Rey Auditory-Verbal Learning Test, TMT A = Trailmaking Test part A, TMT B = Trailmaking Test part B, WCST = Wisconsin Card Sorting Test, Beery VMI = Beery Visual-motor integration test, Rey CFT-copy = copy version of Rey Complex Figure Test, BNT = Boston Naming Test

tion test-speed) and nonverbal long-term memory (Rey CFT-delayed recall). Independently related predictors resulting in better scores were presence of VP shunt, chemotherapy or larger tumor residue in the group with supratentorial hemispheric tumors. Negative predictors were radiotherapy, younger age at diagnosis, older age at assessment, higher BI at diagnosis or assessment, and left-sided tumor (see Table 3).

The same risk factors also were negatively influencing other cognitive domains: radiotherapy (selective attention: Stroop Color-Word test, $p < 0.03$), younger age at diagnosis (performance intelligence: TPIQ, $p < 0.05$), older age at assessment (visual-spatial skills: Rey CFT-copy, $p < 0.05$), higher BI at assessment (language comprehension: Tokentest, $p<0.001$), left-sided tumors (language comprehension: Tokentest, $p<0.001$), and right-sided tumors (performance intelligence: TPIQ, $p <0.001$; visual-spatial skills: Beery VMI, $p = 0.02$). In addition to these

Table 3 Risk factors of the cognitive profile of total group

Neuropsychologic test	R^2	P-value	Predictors	Standardized β coefficients
Cancellation test- fluctuations	0.32	**P<0.001**	Radiotherapy	-0.37
			BI at diagnosis	-0.26
			Age at diagnosis	-0.33
TMT A	0.15	**P<0.05**	BI at assessment	-0.25
			Site of the tumor	-0.28
			VP-shunt	0.13
TMT B	0.26	**P<0.001**	Chemotherapy	0.39
			BI at assessment	-0.35
WCST	0.34	**P<0.03**	Chemotherapy	0.26
			VP-shunt	0.42
			Left/Right localization	0.30
BNT	0.37	**P<0.02**	Age at assessment	-0.33
			VP-shunt	0.14
			Max. diameter residue	0.52

Notes
Max. = maximum, BI = Bicaudate Index, VP-shunt = ventriculoperitoneal shunt, TMT A = Trailmaking Test part A, TMT B = Trailmaking Test part B, WCST = Wisconsin Card Sorting Test, BNT = Boston Naming Test

factors a longer interval between diagnosis and assessment negatively influenced results on tests of language reception (Tokentest, $p<0.04$), selective attention (Stroop Color-Word test, $p<0.04$), and verbal fluency ($p<0.03$). An interaction effect was found between interval diagnosis-assessment and radiotherapy on selective attention ($p<0.01$).

In comparison to the normal population the infratentorial group had significantly lower scores on verbal intelligence (TVIQ, $p<0.02$), sustained attention (Cancellation test-fluctuations, $p<0.001$), speed (Cancellation test-speed, $p<0.001$), long-term visual-spatial memory (Rey CFT-recall, $p<0.001$), executive functioning (TMT A, $p<0.001$; TMT B, $p<0.01$; WCST perseverations, $p<0.001$), and naming (BNT, $p<0.01$). Further sub analysis showed that children with a cerebellar PA had significantly low scores on all these tests with exception of verbal intelligence in comparison to the norms. Children with a brainstem PA had problems with sustained attention (Cancellation test-fluctuations, $p<0.001$), verbal long-term memory (RAVLT delayed recall, $p<0.01$), and naming (BNT, $p<0.02$) in comparison to the norms. Z scores ≤ -2 were found in the domains of speed (Cancellation test-speed, 60%), verbal intelligence (TVIQ<70, 40%), and verbal short-term memory (RAVLT 1-5, 17%).

The supratentorial hemispheric group scored significantly lower on tests measuring selective (Stroop Color-Word test, $p<0.02$) and sustained attention (Cancellation test-fluctuations, $p<0.02$) in comparison to the norms. Z scores ≤ -2 were found in the domains of speed (Cancellation test-speed, 50%), and executive functioning (TMT B, 33%).

The supratentorial midline group performed significantly weaker on speed and sustained attention (Cancellation test-fluctuations and speed, both $p<0.01$) in comparison to the norms. Children with dorsal tumors scored significant lower on language comprehension (Tokentest, $p<0.04$) in comparison to the norms and 25% had Z scores ≤ -2 in verbal short-term memory (RAVLT 1-5)

DISCUSSION

Cognitive deficits are well described in children with a cerebellar PA, but not in a PA in other areas of the brain. This study shows that problems with sustained attention and speed are present in all children with PA. This implies that these cognitive deficits are independent of the site of the tumor and it reflects a more global brain dysfunction.[17] Acquired brain injury in children often has diffuse effects resulting in more basal cognitive function problems.[24,25]

In addition to speed and attention impairments a distinct cognitive profile is found in each defined tumor group. In agreement with our findings in an earlier and smaller series[3] in the infratentorial cerebellar tumor group we find deficits in language, visual-spatial memory, and executive functioning. In another previous study we described long-term social and behavioral problems.[13] The cluster of disturbances of executive function, impaired spatial cognition, linguistic difficulties, and personality changes is often called the cerebellar cognitive affective syndrome (CCAS).[3-7,14] This is thought to be caused by disruption of neural circuits that connect the cerebellum with the prefrontal, posterior parietal, superior temporal and limbic areas.[6]

Traditionally the brain stem is not regarded as a structure that mediates cognitive or behavioral functions. In the brain stem group we recorded deficits in verbal intelligence, verbal memory, naming, and in a previous study[13] behavioral problems. Only in one other study in children with brain stem tumors cognitive deficits restricted to the language domain were described.[26] No significant language disturbances were found in this study, but two children had mild impairments in lexical generation or phonological awareness. In a study comparing adult patients with mild and severe olivo-ponto-cerebellar atrophy, patients with severe atrophy had significantly lower scores on verbal memory (RAVLT).[27] In children with pontine glioma behavioral changes like separation anxiety, school phobia, pathological laughter and aggression have been described.[28] A possible explanation could be disruption of the reciprocal cerebello-ponto-cerebral circuitry resulting in an interruption of fibers modulating behavior and cognition.[27,28]

In the group supratentorial hemispheric tumor we found specific problems with selective attention and executive functioning. This is in contrast to earlier-described general intellectual deterioration and memory dysfunction in children with a hemisphere PA.[7-9] All children in the supratentorial group had normal intelligence and only one child had memory dysfunction due to a resection of the hippocampus. Sparing of global intelligence may be explained by the fact that the children in our supratentorial hemispheric group did not have radiotherapy and epilepsy was well controlled. These factors may lead to intellectual decline and specific memory and attention problems.[29,30]

In the dorsal supratentorial midline tumor group we found specific impairments in the domains of language comprehension and verbal short-term memory. The language and memory problems were recorded in five children with left thalamic tumor localization, and we did not observe apraxia or neglect. These findings are in agreement with the problems of attention, memory, executive and visuospatial functions and the aphasia, transient neglect, and transient apraxia in a small series of five children resected for left thalamic tumors.[31]

The statistical analysis showed that severity of the ventricle dilatation at times of diagnosis and assessment is a risk factor for the development of attention, language comprehension, and executive functioning deficits. Treatment of ventricle dilatation with a VP drain resulted in better scores. This is in agreement with our earlier study in which we computed a correlation between cognitive functioning and preoperative ventricle dilation in children operated for a cerebellar PA.[3] The present finding seems to suggest that treatment of hydrocephalus, even if ventricle width is not progressing, could prevent long-term cognitive deficits after brain tumor treatment, but further research is necessary. Chemotherapy as treatment for PA results in better executive functioning. The effect of radio- versus chemotherapy is well known on cognitive functioning.[29] The more favorable effect of chemotherapy versus surgery may be explained by the fact that in children treated with chemotherapy, surgery was restricted to a diagnostic biopsy or a relatively small resection. This neurosurgical procedure limits the traumatic damage in comparison to a more extensive resection.

This study demonstrates that there are three inter-related age effects: age at diagnosis, interval between diagnosis and assessment, and age at assessment.[32] A younger age at diagnosis as risk factor for more severe impairment of cognitive functions and academic achievement is also described in studies on survivors of childhood cancer[33] and in children with traumatic brain injury.[32] An explanation of this phenomenon could be the vulnerability theory:[33] children with a diagnosis and treatment at a younger age have to learn new skills with already defective basal functions. For the other age effects there could be a biologic[34] or a behavioral explanation.[32] In irradiated children the late effects of radiotherapy on processes interfering with neuronal development lead to cognitive decline[34] and this is supported by the statisti-

cal finding of an interaction effect between age and radiotherapy on attention. However in children without radiotherapy, cognitive problems become apparent years after diagnosis of PA. This finding may be explained by the theory that "early brain damage may have a cumulative effect on ongoing development, with increasing deficits emerging through childhood as more functions are expected to mature and need to be subsumed within the undamaged tissues".[35] This behavioral phenomenon of "growing into deficits" has already been described in children with PA and their functional outcome.[13]

Educational data show a high percentage (59%) of children after PA treatment that needed special education services (special education: 21% and RT: 38%) in comparison to a national average of 5% (special education)[36] and 15% (RT)[37] in the Netherlands. Especially children with a relapse and a younger age at diagnosis are more at risk for educational problems. This is in agreement with the study of long-term survivors of brain tumors in which 24-70% received special education services depending on younger age of diagnosis.[33] In addition to educational problems, these children have also a lower QOL than children in normal education. This strongly suggests that cognitive deficits in children after treatment of PA not only have clinical implications on their school career, but also on their subjective perceptions of daily QOL.

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Chapter 3

Functional outcome after low-grade astrocytoma treatment in childhood.

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ABSTRACT

Objective

The relatively high survival rate of patients with low-grade astrocytoma (LGA) necessitates increasing attention to physical and psychosocial outcome. The objective of the current study was to investigate functional outcomes among children who were treated for low-grade or pilocytic astrocytoma in different areas of the brain.

Methods

Functional outcomes were evaluated in the following domains: impairments, disabilities, handicaps, and Quality Of Life (QOL). In a consecutive series 38 children were included. Follow-up ranged from 3 years and 7 months to 11 years and 4 months after diagnosis.

Results

Approximately 61% of children had impairments and 10% had a severe disability. Handicaps were found in the domains of relationships, school, and behavior. Children who were treated for supratentorial tumors required significantly more special education and children who were treated for infratentorial tumors had significantly more behavioral and social problems. QOL was decreased significantly in all domains except for emotions. Children who had a diagnosis in adolescence reported a lower QOL in social functioning compared with younger children. Data analysis revealed that some deficits suddenly became apparent years after diagnosis.

Conclusion

At long-term follow-up, children who had low-grade or pilocytic astrocytomas were found to have poor functional outcomes, depending on tumor site, age, and relapse. Children without deficits may develop severe cognitive, social, and behavioral deficits years after diagnosis, because of the phenomenon of "growing into deficit". Therefore, the authors suggest a long-term follow-up of children who are treated for a LGA at a young age to detect and subsequently offer support focused on the medical and cognitive impairments as well as on the behavioral and social consequences of their disease.

INTRODUCTION

Brain tumors are the most common solid tumors of childhood. The incidence of these tumors is 3.5 per 100.000 in children below 15 years of age.[1] The most frequently occurring histologic tumor type is the astrocytoma, which is classified according to increasing malignancy grade in pilocytic, fibrillary, and anaplastic astrocytoma. The common variant in children is the pilocytic astrocytoma. This histologic benign tumor type may occur anywhere in the central nervous system but preferred localizations are visual pathways, hypothalamus, and cerebellum.[2]

First-choice treatment for low-grade or pilocytic astrocytoma is total resection. Adjuvant chemotherapy, radiotherapy or both are indicated in case of residual tumor after surgery or tumor relapse. The 5-years survival rate is 80 to 90% and depends on tumor localization and extent of resection.[2]

The relatively high survival rate necessitates increasing attention to physical and psychosocial outcomes. Outcomes in clinical research can be assessed by the five following levels[3]: *disease process*, *impairment* (the general effect of the disease on the child), *disability* (the restriction of the ability to perform tasks within the physical and social environment), *handicap* (the social consequence of these impairments and disabilities in the domains of relationships, school, leisure activities), and *quality of life* (the sense of the child's well-being and life satisfaction in physical, social, and emotional domains).

In children with a low-grade or pilocytic astrocytoma long-term neurologic and endocrine *impairments* frequently occur.[4,5,6] Neurologic impairments include ataxia, visual defects, eye movement disorders, hemiplegia, seizures, hearing loss, and facial palsy.[4] Endocrine impairments are varying combinations of growth hormone deficiency, hypogonadotrophic hypogonadism, hypothyroidism, pubertas praecox, hypoadrenalism, and diabetes insipidus.[5,6]

Disabilities in children with a pilocytic astrocytoma have been studied only in patients with cerebellar localization. Twenty-seven percent of these children develop from long-term *disabilities*.[7]

The social consequences of impairments and disabilities have been described exclusively in adult survivors of childhood brain cancer in general.[8] The *handicaps* in these adults include higher levels of global distress, low household income, low educational attainment, frequently being unmarried, and unemployed. Their *quality of life* (QOL) is significantly lower in the domains of depression and somatization.[8] Just one study specifically evaluated QOL in survivors of childhood cerebellar pilocytic astrocytoma. Medical doctors regard the QOL in this group as "cured and fare well".[9] However, scores on a QOL questionnaire are significantly lower on all scales except for sex life. The scales cognition, well-being, memory, socializing, and adolescence measured the most severe deficits.[9]

This indicates that despite of the benign histology and the favorable survival rate of a low-grade or pilocytic astrocytoma, functional outcome is affected. Firm conclusions, regarding

the pattern or frequency of impairments, disabilities, handicaps, and QOL cannot be drawn from these studies.[4-9] Therefore, to the best of our knowledge we systematically assessed for the first time the functional outcome in all these interrelated domains in children treated for a low-grade or pilocytic astrocytomas in different areas of the brain.

PATIENTS AND METHODS

Patients

Between 1994 and 2000 a consecutive series of forty-two children was treated for a low-grade or pilocytic astrocytoma in our hospital. Two children with neurofibromatosis were excluded because of their specific cluster of deviant behavioral and cognitive impairments[10] and two patients with diencephalic tumors died after a relapse. The remaining thirty-eight patients, sixteen boys and twenty-two girls were included in this study (see Table 1). Informed consent was obtained.

Table 1 Patient characteristics

Characteristics		No. of patients
Sex	Male/ Female	16/22
Age at diagnosis (years)	Mean (Range)	7.0 (1.3-14.7)
Follow-up period (years)	Mean (Range)	7.7 (3.7-11.4)
Tumor localization	Cerebellum	17
	Diencephalon	8
	Brain stem	6
	Optic chiasm	4
	Cerebral hemisphere	3
Histological diagnosis of PA	Cerebellum	17/17
	Diencephalon	4/8
	Brain stem	5/6
	Optic chiasm	2/4
	Cerebral hemisphere	3/3
Primary treatment	Tumor resection	24
	Chemotherapy	8
	Tumor resection and chemotherapy	2
	Tumor resection and radiotherapy	1
	Tumor resection, chemo- and radiotherapy	1
	Radiotherapy	2
First relapses	Number	12
	Mean time (Range)	1.11 (0.4-5.4)

Note PA = pilocytic astrocytoma

Age at diagnosis varied from one year and three months to fourteen years and seven months (mean seven years). The mean follow-up period was seven years and seven months and ranged from three years and seven months to eleven years and four months. Twenty-three children had an infratentorial tumor; seventeen children had a tumor in the cerebellum, five had an exophytic tumor of the medulla oblongata and one an exophytic growing tumor at the mesencephalo-pontine junction. Fifteen children had a tumor with a supratentorial localization. Three of them were situated in a cerebral hemisphere and twelve were midline tumors; eight in the diencephalon and four in the optic chiasm. A histological diagnosis of pilocytic astrocytoma was obtained in thirty-one children. A low-grade astrocytoma was diagnosed on MRI and clinical findings in the remaining children.

Primary treatment consisted of tumor resection in all cerebellar and cerebral tumors. Diencephalic tumors were treated with chemotherapy (5/8), tumor resection (2/8) or tumor resection with adjuvant chemo- and radiotherapy (1/8). Brain stem tumors were treated with tumor resection (2/6), radiotherapy (2/6), chemotherapy (1/6) or tumor resection with adjuvant chemotherapy (1/6). Treatments for optic chiasm tumor were chemotherapy (2/4), tumor resection with radiotherapy (1/4) or tumor resection with adjuvant chemotherapy (1/4). Patients were treated with vincristine and carboplatin according to the Société Internationale d' Oncologie Pédiatrique-Low-Grade Glioma (SIOP-LGG) protocol except one patient with a diencephalic tumor, who was treated twice according to the 8-in-1 protocol.[11] Twelve children (32%) had a first relapse, which was diagnosed four months to five years and four months after the first diagnosis date (mean one year and eleven months). Relapses occurred in two children with a tumor in the cerebellum, three in the brain stem, two in the optic chiasm and five in the diencephalon.

Secondary treatment for these relapses consisted of tumor resection (4/13), chemotherapy (4/13), tumor resection with adjuvant radiotherapy (2/13), tumor resection with adjuvant chemotherapy (1/13), or radiotherapy (1/13). Second relapses occurred in one child with a tumor in the diencephalon four years and ten months after the diagnosis date, and in one child with a tumor in the cerebellum, which was diagnosed six years and two months after the first diagnosis date.

Methods

A pediatric neurologist, a pediatric endocrinologist, and a pediatric neuropsychologist examined all children. The following assessments evaluate the various functional domains:

Impairment

Children were examined neurologically to establish residual impairments. In all children , blood parameters were determined to detect growth hormone (GH) deficiency, thyroid hormone (TH) deficiency, adrenal insufficiency, pubertas praecox, and diabetes insipidus.

Disability

The degree of the disability was scored with the modified Rankin scale and was divided into three categories:[12]

1. No motor or learning disabilities (modified Rankin scale 0). Patient attends regular school.
2. Mild motor disturbances, mild learning disability or both (modified Rankin scale 1 or 2). Patient is able to attend regular school, but needs remedial teaching.
3. Severe motor disturbances, severe learning disability or both (modified Rankin scale 3-5). Patient attends a school for special education or a day care centre.

Handicap

Handicaps were evaluated with a behavior checklist for parents (Child Behavior Checklist; CBCL), for children older than eleven years (Youth-Self Report; YSR) and for teachers (Teacher Record Form; TRF). The scales of the general part of the behavior checklist are activities, relationships and school. The scales of the specific behavioral part are withdrawal, somatic complaints, anxious/depressive, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. Information on the presence of learning disabilities and on actual school situations were obtained from parents and teachers.

Quality of life

Quality of life was assessed with TNO/AZL Children's Quality of Life questionnaires (TACQOL). [13] There is a parent form (TACQOL-P) and a form for children older than eight years (TACQOL-C). Measured scales are physical, motor, autonomy, cognition, social functioning, and positive and negative emotions.

Statistics

Data from the questionnaires were compared with the normative data and corrected for age. To be able to compare the performances, all scores were converted into Z-scores. The Z-score reflects the extent a score deviates from the mean of a normal population. The data were analyzed statistically (SPSS 10.1) with parametric tests (two-sided Students t-test, Independent sample t-test, Paired sample t-test) and non-parametric tests (Mann-Whitney *U* test).

RESULTS

Impairment

At neurologic examination 23 patients showed deficits; 18 had motor problems, 12 had restrictions of visual fields, and eight had reduced vision. None of the children suffered from epilepsy, auditory or somato-sensory deficits (see Table 2). In seven patients endocrine abnormalities were found: four had pubertas praecox, three GH-deficiency, two TSH-deficiency, two ACTH insufficiency, and two diabetes insipidus. All endocrine deficits occurred in children with a supratentorial tumor location except in one. This child with a cerebellar pilocytic astrocytoma had received local irradiation because of a relapse.

Table 2 Medical problems

	Cerebellum N = 17	Diencephalon N = 8	Brain stem N = 6	Optic chiasm N = 4	Cerebral hemisphere N=3
Motor problem	9	4	3	1	1
Epilepsy	0	0	0	0	0
Somatic sensory deficit	0	0	0	0	0
Auditory sensory deficit	0	0	0	0	0
Visual disorder	2	2	0	4	0
Visual field defect	1	5	1	4	1
GH-deficiency	0	1	0	2	0
TSH-deficiency	0	1	0	1	0
ACTH-deficiency	0	1	0	1	0
Pubertas praecox	1	2	0	1	0
Diabetes insipidus	0	2	0	0	0

Disability

Twenty-one patients displayed no disability according to the modified Rankin scale, thirteen a mild disability, and four a severe disability (see Figure 1). Of the total study group 45 % needed special education or remedial teaching, but in children with impairments this percentage was much higher (74%). Mann-Whitney *U* test revealed a significant difference ($p<0.05$) between the Rankin scale and infratentorial versus supratentorial tumor localization. Patients with a supratentorial tumor had higher scores on the modified Rankin scale than patients with an infratentorial tumor. In the group children with impairments there were significantly more children with a supratentorial tumor.

Handicap

Eighty-one percent of the children, 76% of parents, and 57% of teachers completed the behavior checklist. One child did not attend school, because of his young age at the time of this study. The means, standard deviations of Z-scores and the p-values on the behavior

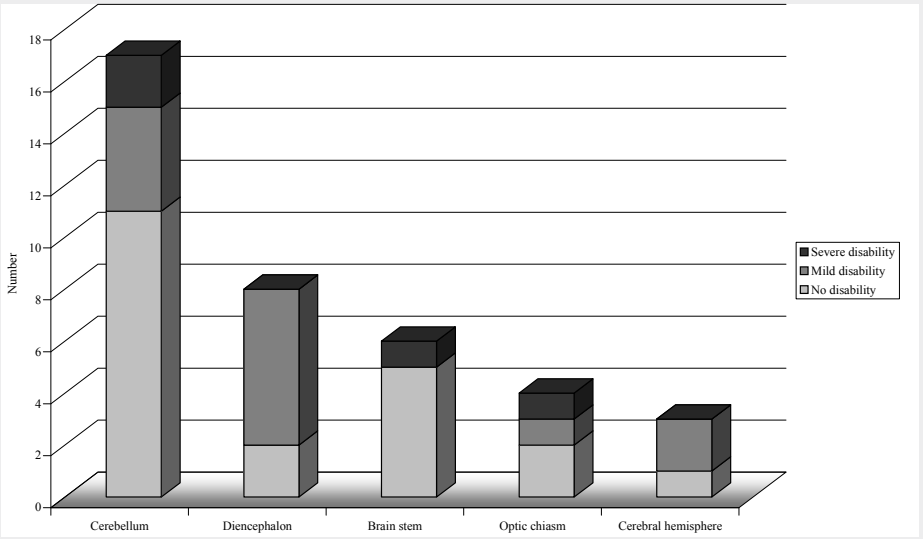

Figure 1 Results on the modified Rankin scale

checklist are represented in Table 3. Student's t-tests revealed that children and parents scored significantly higher on the scales for relationships and school in the general part of the behavior checklist. Parents also indicated a significantly lower number of activities. In the specific behavioral part, parents, children, and teachers scored significantly higher on the scales withdrawal, somatic complaints, anxious/depressive, and social and attention problems. Parents and teachers also scored significantly higher on the scales for rule-breaking and aggressive behavior. The behavior checklists showed that parents and teachers indicate similar behavioral problems. Children reported less behavioral problems than parents and teachers, but still significantly more than healthy, normal children of their age.

Paired samples t-tests revealed differences between parents and teachers on the scales for withdrawal ($t = 2.15$, $p < 0.05$), anxious/depressive ($t = 2.65$, $p < 0.01$), social problems ($t = 2.62$, $p < 0.01$), and attention problems ($t = 2.61$, $p < 0.01$). These results demonstrated that although parents and teachers reported the same behavioral problems they differed in the interpretation of the severity of the problems. A significant difference was found between children and parents on the scale attention problems ($t = 2.32$, $p < 0.05$). Parents considered these attentions problems as more severe than children do.

The results of an independent sample t-test indicated that there were significant differences between patients with infratentorial and supratentorial tumors. Children with infratentorial tumors indicated more problematic behavior on the scales for withdrawal ($t = 2.63$, $p < 0.05$) and somatic complaints ($t = 4.04$, $p < 0.001$). Teachers, but not parents, reported more social

Table 3 Means, standard deviations of Z-scores and p-values on the behavior check

	Parents (CBCL)	P-value	Children (YSR)	P-value	Teachers (TRF)	P- value
Activities	-0.50 ± 1.15	**0.05**	-0.50 ± 1.03	NS	-	-
Relationships	-0.66 ± 1.01	**0.003**	-0.59 ± 1.00	**0.02**	-	-
School	-0.89 ± 0.84	**0.0001**	-	-	-0.15 ± 0.71	NS
Withdrawal	-0.71 ± 0.88	**0.0001**	-0.44 ± 0.72	**0.02**	-0.33 ± 0.47	**0.004**
Somatic complaints	-0.95 ± 1.02	**0.0001**	-0.67 ± 0.70	**0.001**	-0.55 ± 0.81	**0.006**
Anxious/ depressive	-0.56 ± 0.74	**0.0001**	-0.30 ± 0.54	**0.04**	-0.22 ± 0.34	**0.008**
Social problems	-0.84 ± 0.86	**0.0001**	-0.45 ± 0.55	**0.004**	-0.35 ± 0.46	**0.003**
Thought problems	-0.05 ± 0.59	NS	-0.02 ± 0.51	NS	-0.02 ± 0.50	NS
Attention problems	-0.68 ± 0.80	**0.0001**	-0.40 ± 0.68	**0.03**	-0.28 ± 0.57	**0.03**
Rule-breaking behavior	-0.33 ± 0.54	**0.003**	-0.09 ± 0.20	NS	-0.14 ± 0.27	**0.02**
Aggressive behavior	-0.29 ± 0.55	**0.008**	-0.09 ± 0.30	NS	-0.28 ± 0.47	**0.01**

Notes
CBCL = Child Behavior Checklist, YSR = Youth Self Report, TRF = Teacher Report Form, NS = not significant, - = not tested in this form

problems (t = 3.65, p < 0.002) in children with infratentorial tumors. Children with a relapse indicated significantly more social problems than children without a relapse (t = 2.9, p<0.01).

Quality of life

Ninety-five percent of children, and 92% of parents completed the TACQOL. Parents and children indicated significantly more motor, cognitive, and social problems than normal children. Parents also registered physical and autonomy problems. The means, standard deviations of Z-scores, and p-values are summarized in Table 4. Results of the paired sample t-test revealed significant differences on the scales for physical (t = 3.69, p < 0.01), motor (t = 4.46, p < 0.001), and autonomy (t = 2.66, p < 0.05) between parents and children. Parents judged the quality of life poorer in these domains than children. Independent sample t-test did not show significant differences noted between the infratentorial and supratentorial tumor groups, but there were significant differences between the children with and those without relapses. Parents of children with a relapse reported a decreased QOL in the scale autonomy (t = 2.5, p < 0.05).

Table 4 Means, standard deviations of Z-scores and p-values on the TACQOL

	Parents TACQOL-P	P-value	Children TACQOL-C	P-value
Physical	-0.90 ± 1.70	**0.004**	-0.01 ± 1.29	NS
Motor	-2.89 ± 3.17	**0.0001**	-1.36 ± 2.16	**0.002**
Autonomy	-2.22 ± 3.66	**0.001**	-0.74 ± 2.14	NS
Cognition	-1.22 ± 1.78	**0.0001**	-0.72 ± 1.59	**0.02**
Social	-0.78 ± 1.86	**0.02**	-0.71 ± 1.46	**0.02**
Positive emotions	-0.52 ± 1.60	NS	-0.32 ± 1.21	NS
Negative emotions	0.27 ± 1.45	NS	0.15 ± 1.35	NS

Note
NS = not significant

DISCUSSION

This study evaluated impairments, disabilities, handicaps, and QOL in 38 children treated for a pilocytic or low-grade astrocytoma. Sixty-one percent of children presented with neurologic or endocrine impairments. Forty-five percent of all children had long-term mild or severe disabilities and needed special education or remedial teaching. This percentage far exceeded the national average of 5% in the Netherlands.[14] Statistical analysis revealed a difference in the severity of the disabilities in the infratentorial and the supratentorial tumor group, 30% versus 73%. The percentage of disabilities in our infratentorial tumor group is comparable with the 27% disabilities in another study[7]. Disabilities in the supratentorial group have to the best of our knowledge as yet not been reported. Because of a relationship between presence of impairments and percentage of disabilities, the high percentage in the supratentorial group is not surprising as they have relatively more visual impairments. So we conclude that especially in children with a supratentorial tumor, the visual impairments will act on academic functioning.

The social consequences of impairments and disabilities, i.e. the handicaps, were evident in the domains of relationships and behavior. Children in this study did not mix with friends and developed fewer activities outside school. These psychosocial problems are in accordance with those displayed by survivors of childhood cancer in general.[8] Children, parents and teachers equally consider the internalizing behavior problems such as withdrawal, somatic complaints (without medical cause), and the social problems as most severe. They are more pronounced in the infratentorial than in the supratentorial tumor group.

A wide variety of long-term behavioral disturbances has been described in 60% of survivors of cerebellar pilocytic astrocytoma.[15] One of the most striking examples of withdrawal is verbal hypospontaneity with flattened affect. The children do not speak spontaneously and are reluctant to engage in conversation. [15] The hypospontaneity, which is observed at long-term follow-up may fit in the spectrum of cerebellar disorders of spontaneous speech such as mutism and subsequent dysarthria[16] (MSD), or the posterior fossa syndrome.[17] The MSD syndrome consists of transient short-term mutism followed by dysarthria, which gradually resolves over months. The posterior fossa syndrome includes MSD, but also comprises oropharyngeal dyspraxia, emotional lability, incontinence, and bizarre personality changes. When verbal hypospontaneity is not associated with postoperative mutism it may be a faint expression of this spectrum of spontaneous cerebellar speech disorders. This verbal hypospontaneity is thought to be caused by a dysfunction of the cerebro-cerebellar loops connecting the cerebellum with the prefrontal cortex.[18]
Children, parents, and teachers rate behavior problems differently. Parents and teachers indicate behavior problems more frequently than children, although, in survivors of child-

hood alcancer a marked concordance between mothers and children is described.[19] Other studies emphasize the many factors that must be taken into account, such as personality, status of treatment, parental status, and single parent families.[20] The different ratings in our study also may also be explained by what is often being referred to as 'resilience' and can also be described as coping or adaptation to impairments. This is supported by the fact that survivors of childhood cancer tend to judge their own ability to cope as superior.[21]

Parents report a decreased QOL in all scales except for positive and negative emotions. Children indicate a low QOL in motor, cognitive and social functioning. The low QOL in our study was similar to that displayed by survivors of a cerebellar pilocytic astrocytoma.[9] A Pearson correlation matrix analysis revealed significant correlations between age at diagnosis and QOL in social functioning (TACQOL-C: r = -0.57;TACQOL-P: r = -0.37). Children who were diagnosed during adolescence report a lower QOL in social functioning than children who were diagnosed at a younger age. This reflects the overall importance of establishing socializing and intimate relationships during adolescence.

This study also found significant correlations between age at the time of assessment and behavior (withdrawal; r = -0.50), and QOL (physical condition; r = -0.43, motor; r = -0.45, cognitive; r = -0.53, social functioning; r = -0.40). These correlations seem to suggest that behavioral, physical, motor, cognitive, and social problems become more manifest over the years. A more developed sense of self-reflection cannot be held responsible for these relations, because parents also signal more problems when their children reach adolescence. Rather it seems that some of these problems suddenly become apparent years after the diagnosis and the treatment. It has been suggested that "early brain damage may have a cumulative effect on ongoing development, with increasing deficits emerging through childhood as more functions are expected to mature and need to be subsumed within the undamaged tissues".[22, p 107] These new long-term problems could result from changes during the further postnatal development leading to disruption in pathways that fail to develop properly as a result of the tumor or surgical lesion.[15]

This phenomenon of "growing into deficits" may have played a role in the development of long-term deficits. This is illustrated by the following two patients, which were operated at primary school age for a cerebellar pilocytic astrocytoma. One girl obtained excellent results throughout primary school and functioned socially well. At secondary school she became very depressive and was not able to maintain friendships. She developed a habit of auto mutilation and regularly cut into arms, legs and back. She tried to kill herself twice by cutting her wrists and jumping off a roof. The other girl also obtained good school results at primary and in the first three grades of secondary school, and she did not experience any social problems. In the fourth grade of secondary school, she started to stalk men she liked. Later, she became sexually hyperactive and wrongly accused family members of sexual abuse. Medical examination and police investigation did not find evidence of the rather bizarre accusations. Both patients were treated by a psychiatrist and were counseled by a psychotherapist.

Children who have pilocytic or low-grade astrocytomas have a high survival rate, and from oncological point of view, a good prognosis. However at long-term follow-up, they display impairments, disabilities, handicaps, and a low quality of life depending on tumor site, age, and relapse. Especially children who are diagnosed in adolescence are vulnerable in terms of social problems. More important is that children without deficits may develop severe cognitive, social, and behavioral deficits years after diagnosis because of the phenomenon of "growing into deficit". Therefore, we advise a very long-term follow-up of children, even when they have been treated for a low-grade or pilocytic astrocytoma at a young age and do not experience any severe disabilities in the first years after diagnosis, to detect and offer adequate and timely intervention programs focused on the medical and cognitive impairments as well as on the behavioral and social consequences of their disease.

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Chapter 4

Long-term outcome in children with low-grade tectal tumors and acquired obstructive hydrocephalus

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Submitted

ABSTRACT

Objective

To study long-term neurologic, cognitive and behavioral deficits in children with a low grade tectal tumor and acquired obstructive hydrocephalus.

Method

In a consecutive series of 12 children with low-grade tectal tumor diagnosed in our hospital between 1994-2008 neurologic, neuropsychologic, and radiologic data were prospectively collected. Intelligence, memory, attention, language, visual-spatial, and executive functions were assessed. Follow-up ranged from 1 year to 10 years.

Results

At follow-up, most frequent neurologic disability was fatigue in children with a low-grade tectal tumor. They scored lower on sustained attention, long-term memory and had more behavioral problems. Factors influencing cognition were duration of symptoms of raised intracranial pressure (ICP) and persisting severe hydrocephalus. The cognitive problems resulted in 60% of children needing assistances of special services at school.

Conclusion

At long-term, children with a low-grade tectal tumor display invalidating neuropsychologic impairments resulting in educational problems. Adequate and timely treatment of hydrocephalus may result in better cognitive functioning. Our findings suggest that part of the symptoms of the cerebellar cognitive affective syndrome may not have resulted from a cerebellar lesion itself but rather from a cerebral dysfunction or compression of supratentorial structures in the cerebello-cortical circuitry partly due to the obstructive hydrocephalus.

INTRODUCTION

Brain stem tumors account for 10 to 25% of pediatric brain tumors.[1,2] Low grade glial tumors of the tectum are a distinct subgroup and occur in 5% of children with a brainstem tumor.[2] They are relatively benign, tend to have an indolent course, and are associated with a good long-term survival.[3-5]
Children typically present with clinical symptoms of raised intracranial pressure (ICP) due to obstructive hydrocephalus when tumor obliterates the Sylvian aqueduct. Associated symptoms due to pressure on tectal plate or brain stem structures may occur such as headache, visual impairment, pyramidal symptoms, ataxia, nystagmus, Parinaud syndrome, sixth nerve palsy, tremor, head bobbing, weight loss, macropsia, or diplopia.[1-10] Also cognitive problems at onset such as memory deficits, declining school performance, change of personality, developmental delay, and dysphasia have been described.[2-8]

On MRI, tectal plate tumors show as hypo- or isointense on T1 weighted images, hyperintense on T2 weighted images. Enhancement with gadolinium rarely occurs.[6] These MRI characteristics are quite specific and rarely pathological verification of tumor is required. Treatment is in most cases limited to alleviation of hydrocephalus by a ventriculo-peritoneal (VP) shunt or endoscopic third ventriculostomy (ETV). [1-5, 7-9] Surgical treatment of the tumor or adjuvant radiotherapy is reserved for progressive or recurrent disease. In only 13-38% of patients progression of the tumor occurs.[1,2,4-6,8] Predictors are tumor size and enhancement on MRI.[1,3,5,6]

After treatment, the degree of disability is no to mild measured by the Karnofsky score.[4] Observed cognitive deficits are attention deficits, learning disabilities, and memory deficits,[5-7] but formal neuropsychologic assessment of cognitive deficits has not been systematically performed to the best of our knowledge in children with low-grade tectal plate tumors and obstructive hydrocephalus.

Cognitive deficits have been well studied in children treated for congenital hydrocephalus. In children with spina bifida who were treated for congenital hydrocephalus, intelligence is in the average, low-average, or borderline range.[11] They may have problems with arithmetic, visual and tactile perception, motor speed, and visual-motor integration.[11] Children with a congenital aqueduct stenosis have a lower non-verbal Intelligence Quotient (IQ), borderline mean IQ, and residual motor problems after treatment.[12] It has been suggested that in the latter children the cluster of cognitive deficits is comparable with that of the Non-verbal Learning Disabilities (NLD) syndrome.[13] NLD is characterized by impairments in three cognitive domains: visual/spatial/organizational, sensorimotor, and social functioning.[13]

The purpose of the present study was to prospectively assess long-term neurologic, cognitive and behavioral deficits in children with a low-grade tectal tumor and obstructive hydrocephalus in a small consecutive pediatric series.

PATIENTS AND METHODS

Patients

Between 1994 and 2008, a consecutive series of 12 children had a diagnosis of low grade tectal tumor at Erasmus Medical Centre/Sophia Children's hospital. One of them had a subtotal resection of a pilocytic astrocytoma in another hospital, but follow-up was done in our hospital. All twelve patients (two boys) could be tested according to our standard neuropsychologic follow-up protocol according to the Dutch Child Oncology Group. In one child only neurolinguistic assessment was done.

Methods

All children had a standardized pediatric neuro-oncologic and neuropsychologic follow-up in a multidisciplinary outpatient clinic after diagnosis and initial treatment. A pediatric neurologist examined all children to establish residual neurologic impairments and to determine academic achievement at time of neuropsychologic assessment. The modified pediatric Rankin scale (mRS) was used to assess the degree of disability[14]:

- mRS 1: No motor or learning disabilities (Rankin scale 0). Patient attends regular school.
- mRS 2: Mild motor disturbances, mild learning disability or both (Rankin scale 1 or 2). Patient is able to attend regular school, but needs remedial teaching.
- mRS 3: Severe motor disturbances, severe learning disability or both (Rankin scale 3-5). The child attends a school for special education or a day care centre.

MRI or CT scans at diagnosis with and without contrast enhancement were reviewed for ventricle width, and the preoperative size and site of the tumor. MRI scans at time of neuropsychologic assessment were used to determine the ventricle width, presence of VP-shunt or ETV, presence and size of residual tumor. We computed the bicaudate index (BI) as a measure of ventricular dilatation at presentation and at time of assessment.[15] We distinguished: no (BI < 0.19), mild (BI 0.19-0.26), and severe hydrocephalus (BI > 0.26).[15]

Cognitive tests and behavioral questionnaires developed for children and young adults were administered to assess skills in seven domains[16,17]:

1 Intelligence: age-appropriate Dutch version of the Wechsler Scales for Intelligence (FSIQ = total intelligence, TVIQ = verbal intelligence, TPIQ = performance intelligence).
2 Memory: Rey Auditory-Verbal Learning Test (RAVLT), Delayed recall version of Rey Complex Figure Test (Rey CFT- delayed recall).
3 Language: Boston Naming Test (BNT), Tokentest.
4 Visual-(spatial): copy version of Rey Complex Figure Test (Rey CFT-copy), Beery Visual Motor Integration test (VMI).
5 Executive skills: Trailmaking Test (TMT), Verbal Fluency, Wisconsin Card Sorting Test (WCST).
6 Attention: Stroop Color-Word Test (Stroop) and Cancellation Test
7 Behavior: Child Behavior Checklist (CBCL) and Youth Self Report (YSR).

All tests and questionnaires were administered in their Dutch versions. Manifest neuropsychologic deficits, spontaneous language and speech were judged by a pediatric clinical neuropsychologist. Behavioral disturbances were evaluated from observation of the child and interviews with the parents according to criteria of the Diagnostic and Statistical Manual of mental disorders 4th Edition (DSM IV). The results of observation and interviews were discussed in a multidisciplinary team.

Statistics

The data of the neuropsychologic assessment were compared with the normative data of the Dutch population and corrected for age. In order to compare the performances of all children, scores were converted into Z-scores. Because of the small sample size not all subscales of the CBCL and YSR were analyzed and analysis was limited to the subscales internalizing behavior, externalizing behavior, and total problems. The χ^2 test was used to compare variance of our study group with the normal population. The Kolmogorov-Smirnov test was used to control for normal distribution. Data that did fulfill the requirements of parametric testing were analyzed with two-sided Students t test. And correlations were computed with a two-sided Pearson correlations matrix (SPSS 17.0).

RESULTS

Neurologic data

Table 1 shows patient characteristics at times of diagnosis and assessment. Median age at diagnosis was 10 years and 2 months (range 3 months – 17 years and 4 months). All tumors were iso- or hypointense on T1-weighted and hyperintense on T2-weighted MRI images. Gadolinium enhancement was observed in three patients. A low-grade astrocytoma was diagnosed based on MRI characteristics in nine children. At diagnosis, one tumor was > 2 cm and invaded nearby structures (patient 12). Biopsy confirmed a neurocytoma and no

Table 1 Clinical characteristics

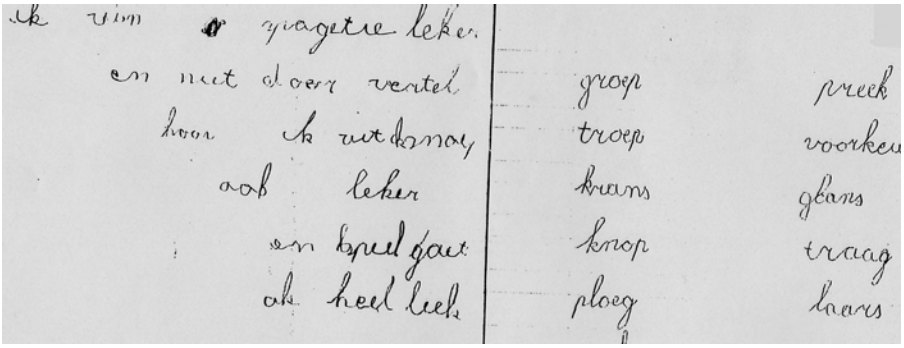
Pat	Age at diagnosis y.m	Age at testing y.m	Interval diagnosis-test y.m	Duration of signs of ICP	BI	Treatment	PD	Max diam tumor cm	Enhancement on MRI
1	6.11	16.6	9.7	0 months	Pre: 0.31 Post: 0.14	ETV	PA	Pre: 1.00 Post: 1.20	No
2	11.00	20.5	9.5	18 months	Pre: 0.29 Post: 0.07	VP shunt		Pre: 1.20 Post: 2.43	No
3	0.3	8.2	7.11	2 months	Pre: 0.42 Post: 0.20	ETV/ VP shunt		Pre: 0.21 Post: 1.06	No
4	8.2	13.4	5.2	6 months	Pre: 0.34 Post: 0.26	VP shunt		Pre: 0.60 Post: 0.60	No
5	7.10	12.5	4.7	6 months	Pre: 0.29 Post: 0.15	ETV		Pre:1.39 Post: 1.39	No
6	16.3	18.5	2.2	24 months	Pre: 0.30 Post: 0.32	ETV		Pre: 1.50 Post: 1.75	No
7	13.0	14.8	1.8	0 months	Pre: 0.29 Post: 0.16	ETV		Pre: 1.25 Post: 1.07	No
8	9.3	10.5	1.2	3 months	Pre: 0.27 Post: 0.18	ETV	GG	Pre: 1.60 Post: 2.26	Yes
9	14.8	15.9	1.1	2 months	Pre: 0.30 Post: 0.15	ETV	PA	Pre: 1.72 Post: 2.49	Yes
10	11.7	14.9	3.2	24 months	Pre: 0.33 Post: 0.28	ETV		Pre: 1.21 Post: 1.16	Yes
11	17.4	18.4	1.0	24 months	Pre: 0.30 Post: 0.28	ETV		Pre: 0.70 Post: 1.83	No
12	5.0	7.4	2.4	6 months	Pre: 0.35 Post: 0.18	VP shunt	NC	Pre: 3.4 Post 3.6	No

Notes

y = years, m = months, max = maximum, diam = diameter, cm = centimeter, BI = Bicaudate Index, pre = before treatment of hydrocephalus, post = at moment of assessment, ETV = endoscopic third ventriculostomy, PD = pathological diagnosis, PA = pilocytic astrocytoma, GG = ganglioglioma, NC = neurocytoma

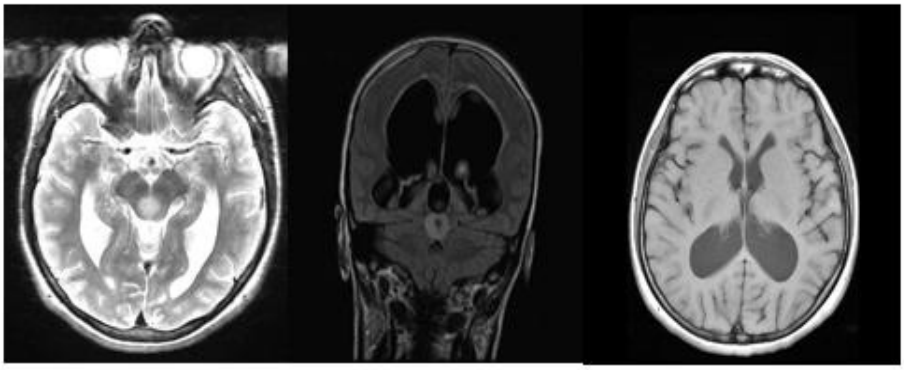
additional treatment was necessary. In patients 1 and 9, a neuropathological diagnosis of pilocytic astrocytoma was confirmed after subtotal resection or biopsy. In two of the three patients (patients 8, 9) with tumor enhancement and in three of nine patients (patients 2, 3, 11) without tumor enhancement, radiological progression was detected during follow-up. Statistical analysis revealed no relation between Gadolinium enhancement and radiologic progression. In patient 8 clinical symptoms and signs progressed and she was treated with partial resection and stereotaxic radiotherapy. The neuropathological diagnosis was a ganglioglioma. The other four patients had no clinical symptoms and further follow-up revealed stable disease or smaller size of the tumor on follow-up MRI.

At diagnosis, median tumor diameter was 1.23 cm (range 0.21 – 3.40 cm). Two children did not have clinical symptoms of raised ICP. Their tumors were discovered by chance on CT after neurotrauma (patients 1 and 7). In the other children, the median duration of symptoms of



Left **Right**

Figure 1 *Left:* Neglect before ETV *Right:* Neglect after ETV



A **B** **C**

Figure 2 Patient 5. *A:* Transversal T2-weighted MRI image showing a hyperintense periaqueductal tumour lesion *B:* Coronal section of a MRI Flair image of a tectal plate tumour and obstructive hydrocephalus before ETV C: Transversal T1-weighted MRI image of the same patient after ETV

raised ICP before diagnosis was six months (range 2 – 24 months). Presenting symptoms of these patients were headache (83%), visual problems (75%), motor problems (67%), vomiting (42%), seizures (33%), memory deficits (25%), declining school performances (25%), personality change (16%), hormonal dysfunction (16%), tremor of the hand (8%), lethargy (8%), neglect (8%, see Figure 1 and Figure 2), disorientation (8%), abnormal increase of skull circumference (8%), and binge eating (8%).

All children had a severe hydrocephalus at first presentation (Median pre-treatment BI = 0.30, range 0.27-0.42). A VP-shunt was inserted in three children and nine children were initially treated with ETV. In the youngest child (patient 3), a VP shunt was inserted after multiple non-functioning ETV's. At time of assessment seven children had no, two mild and three severe

hydrocephalus (Median post-treatment BI = 0.18, range 0.07-0.32). None of the children had clinical symptoms of raised intracranial pressure. At follow-up, 11 children still had neurologic symptoms or impairments: headache (25%), impairment of vertical eye movements (25%), disinhibited behavior (16%), tremor of the hand (8%), and epilepsy (8%). In addition, 50% of children suffered from fatigue.

At time of diagnosis, all children except patient 10 had a normal psychomotor development. At time of assessment, 58% of children had a mild or severe disability on the mRS. Twenty five percent of children needed special education and 33% of the children received remedial teaching (RT) by a specialized Dutch institution. In six patients there were learning disabilities: three children had reading problems and three children had problems with arithmetic.

Neuropsychologic data

Median age at assessment was 14 years and 8 months (range 7 years and 5 months – 20 years and 5 months). The median follow-up period was 2 years and 9 months (range 1 year – 9 years and 7 months). In patient 2 neurolinguistic assessment was done (including verbal memory, BNT, and Tokentest).

At follow-up two children had a mild mental retardation (IQ range 55 - 70 according DSM IV diagnosis). In comparison with the normal population (Table 2), the group showed weaker performances on tests measuring attention (Cancellation test-fluctuations, $P < .001$), long-term memory (Rey CFT-delayed recall, $P = .01$; RAVLT delayed recall, $P = .002$), and behavior (CBCL internalizing behavior, $P = .05$; CBCL total problems, $P = .004$). Further analysis seems to suggest that severity of hydrocephalus at time of assessment with a longer period of raised ICP influenced neuropsychologic functioning. Correlations were found between severe hydrocephalus at time of assessment and a long period of raised ICP scored and tests measuring intelligence (TVIQ, $r = -.61$, $P = .05$;FSIQ, $r = -.60$, $P = .05$), speed (Cancellation test – speed, $r = -.73$, $p = 0.01$) , memory (Rey CFT – delayed recall, $r = -.69$, $P = .02$), executive functioning (TMT B, $r = -.66$, $P = .03$), and behavior (YSR total problems, $r = -.97$, $P = .03$). See table 2.

DISCUSSION

Low grade tumors of the tectum are a distinctive subgroup of pediatric brainstem tumors with an indolent course and good survival rate.[3-5] They become symptomatic by obliterating the Sylvian aqueduct and causing acquired obstructive hydrocephalus. Treatment is in most children limited to alleviation of hydrocephalus by a VP shunt or ETV. Hence they could be a model for the effect of acquired hydrocephalus on long-term cognition and behavior in children and young adults.

Table 2 Neuropsychologic outcome in IQ and Z scores

	Neuropsychologic tests	Total group (N = 12)
Intelligence	FSIQ	93 ± 19
	TVIQ	92 ± 19
	TPIQ	94 ± 21
Attention	Stroop Color-Word test	-0.79 ± 1.74
	Cancellation-test-speed	-0.95 ± 1.66
	Cancellation-test fluctuations	**-2.20 ± 1.11****
Memory	Rey CFT- delayed recall	**-1.21 ± 1.27****
	RAVLT 1-5	-0.53 ± 1.23
	RAVLT delayed recall	**-0.77 ± 0.62****
Executive skills	TMT A	-0.38 ± 1.51
	TMT B	-0.15 ± 1.38
	Verbal fluency	-0.18 ± 1.28
	WCST perseverations	-0.30 ± 0.35
Visual-spatial skills	VMI	-0.41 ± 1.61
	Rey CFT- copy	-0.40 ± 1.28
Language	Token test	-0.29 ± 1.34
	BNT	-1.82 ± 3.19
Behavior	Internalizing problems (CBCL)	**-0.99 ± 1.25***
	Externalizing problems (CBCL)	-0.20 ± 0.69
	Total problems	**-0.93 ± 0.71****
	Internalizing problems (YSR)	0.43 ± 0.48
	Externalizing problems (YSR)	0.80 ± 0.97
	Total problems	0.08 ± 1.14

Notes
SD = standard deviation , ** = p≤0.01 in comparison to normative data, * = p≤0.05 in comparison to normative data, FSIQ = total intelligence, TVIQ = total verbal intelligence, TPIQ = total performance IQ, Rey CFT-delayed recall = delayed recall version of Rey Complex Figure Test, RAVLT = Rey Auditory-Verbal Learning Test, TMT A = Trailmaking Test part A, TMT B = Trailmaking Test part B, VMI = The Beery Developmental test of Visual-Motor Integration, WCST = Wisconsin Card Sorting Test, Beery VMI = Beery Visual-motor integration test, Rey CFT-copy = copy version of Rey Complex Figure Test, BNT = Boston Naming Test, CBCL = Child Behavior Checklist, YSR = Youth Self Report.

Hydrocephalus

In our study we did not find a difference in cognitive or behavioral outcome in children with either a VP shunt or ETV. We did however find a correlation between good cognitive and behavioral functioning and normalization of ventricle size independent of the intervention used to alleviate hydrocephalus. In one of our earlier studies we also found a relation between severity of obstructive hydrocephalus at diagnosis and visual-spatial dysfunctions in children with a cerebellar tumor.[15] Also a longer period of raised ICP negatively influenced cognition and behavior. In all children, neurosurgical intervention was aimed at reduction of ventricle size. Despite maximal treatment, hydrocephalus persisted especially in children with a long history of symptoms of raised ICP. This implies that persistence of wider ventricles could be a predictor of poor neuropsychologic functioning in children with acquired obstructive hy-

drocephalus and a tectal glioma. This is in agreement with the finding in adult patients with aqueduct stenosis that cognitive recovery correlates well with the reduction in ventricular size.[18] The above findings seem to suggest that it is important to decrease ventricular size as much and as soon as possible also in children who do not have clinical symptoms or signs of raised ICP in order to obtain an optimal condition for a good cognitive development. However, optimal treatment of hydrocephalus did not prevent persisting memory and attention problems in the group of children with normal ventricle size. This raises the question whether these remaining symptoms were a result of long lasting effects of raised ICP before diagnosis or were caused by the tectal tumor.

Cognitive and behavioral problems

In patient five we found a left-sided visual neglect as a presenting symptom, which had disappeared 3 months after ETV. Usually a supratentorial lesion in the right parietal lobe or right frontal damage of the gyrus cinguli or the basal nuclei are associated with signs of left-sided neglect.[19] Neglect has never been described in children with a congenital or an acquired hydrocephalus due to a tectal tumor. The colliculus superior is part of the tecto-pulvinar circuitry regulating spatial attention in the visual fields. In cat and rat unilateral damage to the colliculus superior may cause contralateral neglect. Cats with unilateral striatal, dorsal and ventral extrastriatal cortical damage do not orient to contralateral visual stimuli. Orientation can be restored by ablating the contralesional superior colliculus or the intertectal commissure. In animals this phenomenon is known as the Sprague effect.[20] One adult with a tectal plate tumor developed a left-sided neglect after a right frontal lesion due to removal of a frontal ventricular shunt. The neglect disappeared after damage of the left colliculus superior due to destruction by a tumor cyst. This demonstrates that the Sprague effect extends to humans.[21] In patient 5, the tectum glioma had invaded both superior colliculi equally (Figure 2) and treatment of the tumor was not considered necessary. However, the ETV procedure was uncomplicated but carried out by entering the ventricles though the right frontal cortex suggesting that also in this child alleviation of the neglect was unintentionally caused by the frontal lesion.

Our findings of persisting memory, attention, and behavioral problems in these children are in agreement with lowered intelligence, memory, attention and learning disabilities in three small observational studies.[5-7] In two out of five pediatric patients with a tectal tumor below average cognition and memory disturbances were observed.[7] In three out of twelve children with resection or radiotherapy for a tectal plate tumor, two had mild learning disabilities and one had a mild attention deficit.[6] In another study, two out of 11 patients had persisting impairment in verbal memory.[5] No information was available on ventricular sizes in the children of these latter two studies. The brainstem is not regarded as a structure that mediates cognitive functions. However, also in an earlier study we recorded deficits in verbal intelligence,

verbal memory, and naming in children with low-grade non-tectal brain stem gliomas.[16] Only in one other study in children with brain stem tumors, language deficits were described.[22] In the present study, we exclusively found with further statistical analysis significant language disturbances in children with severe hydrocephalus at time of assessment. This suggests that not the location of the tumor, but rather the severity of the hydrocephalus seems to play a role in language impairments in children with a tectal tumor.

At follow-up, we found behavioral disturbances and in adulthood, two patients needed psychotherapy because of an anxiety disorder. No behavioral disturbances are mentioned in earlier pediatric series with tectal plate tumors, which often invade the dorsolateral peri-aquaductal grey matter. The periaqueductal grey is known to be part of a fear network which further consists of the central nucleus of the amygdala, ventromedial hypothalamus (VMH), and hippocampus. Deep brain stimulation in rats of the dorsolateral periaqueductal grey and one of its target structures, the VMH has been shown to induce escape behavior that mimics a panic attack in humans.[23]

Also in children with congenital hydrocephalus behavioral problems are common. These children have problems with social skills, attention with hyperactivity, and comprehension of nonverbal cues consistent with NLD syndrome.[13] Persisting somatic complaints, social and behavioral problems have also been documented in children with low grade astrocytoma of the cerebellum.[14] In these children the behavioral problems are considered to be part of the Cognitive Cerebellar Affective Syndrome (CCAS), which is a cluster of disturbances of executive function, impaired spatial cognition, linguistic difficulties, and personality changes.[24] The problems with executive, spatial, linguistic, and behavioral functioning are very similar to those of our group of children with a severe hydrocephalus at time of assessment. Our findings suggest that part of the symptoms that have been attributed to CCAS in children with cerebellar tumor may not have resulted from the cerebellar lesion due to resection or the tumor itself but rather from a cerebral dysfunction or direct compression of supratentorial structures involved in the cerebello-cortical circuitry as a result of the obstructive hydrocephalus.

Conclusions

At long-term, children with a low-grade tectal tumor display invalidating cognitive and behavioral impairments resulting in educational problems. A persisting severe hydrocephalus and a longer period of raised ICP seem predictors for a worse cognitive and behavioral outcome. Rigorous and timely treatment, if technically possible, of acquired hydrocephalus to prevent most of the cognitive sequelae is advocated. Our findings suggest that part of the symptoms of CCAS may not have resulted from a cerebellar lesion itself but rather from a cerebral dysfunction or compression of supratentorial structures in the cerebello-cortical circuitry due to the obstructive hydrocephalus.

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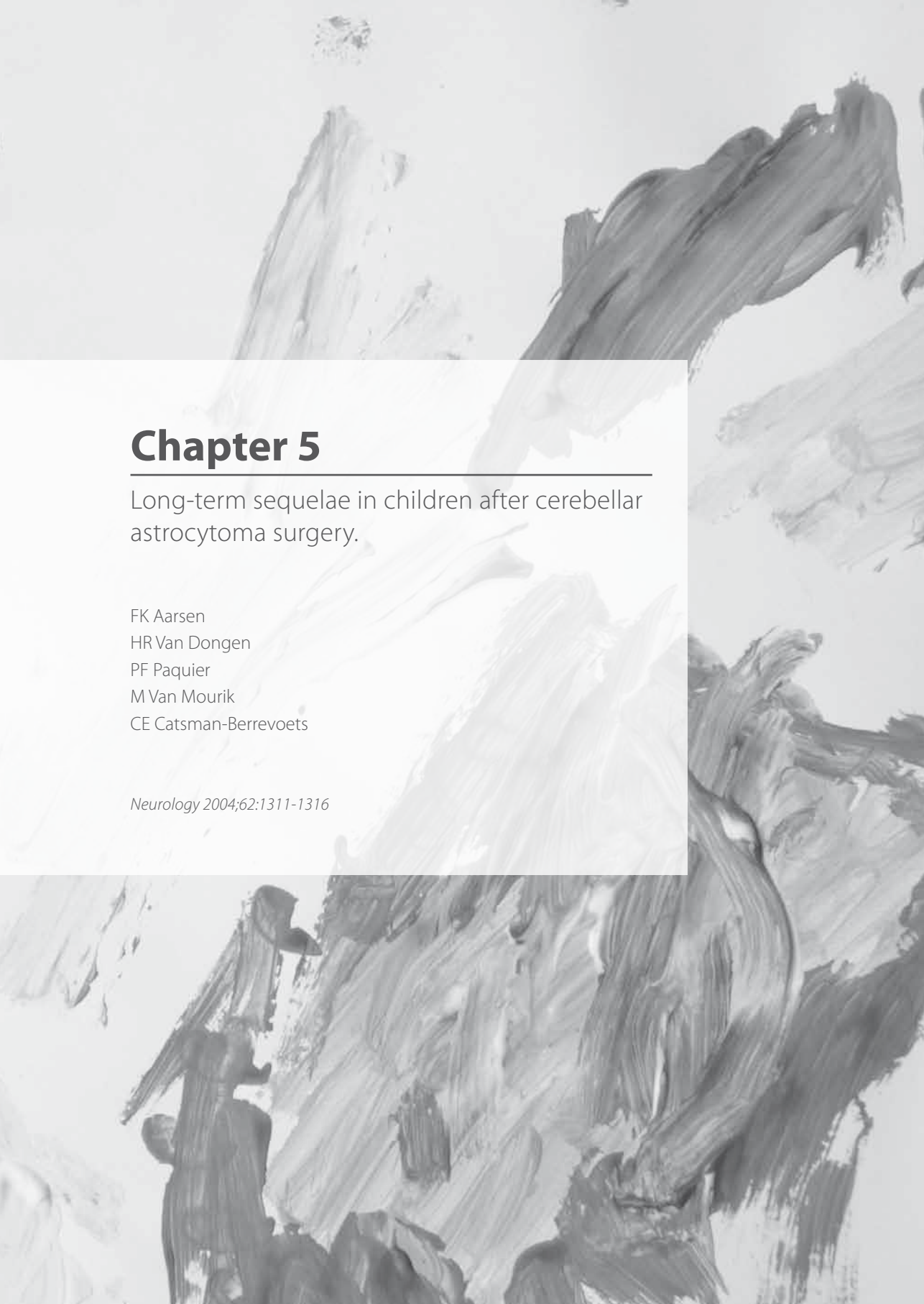

Chapter 5

Long-term sequelae in children after cerebellar astrocytoma surgery.

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Neurology 2004;62:1311-1316

ABSTRACT

Objective

To study long-term effects on neurologic, neuropsychologic and behavioral functioning in children treated for Cerebellar Pilocytic Astrocytoma (CPA) without additional radio-and chemotherapy.

Methods

The authors assessed speech, language, nonverbal intelligence, attention, memory, executive skills and visual (-spatial) functions in a consecutive series of 23 children. Neurologic and neuropsychologic follow-up ranged from 1 year to 8 years and 10 months after resection.

Results

Long-term sequelae in the investigated domains were found in all children. Apraxia, motor neglect, dysarthric features, as well as language, sustained attention, visual-spatial, executive, memory, and behavioral problems were observed in various combinations and to different degrees. No clear pattern of neurocognitive disturbances could be discerned in this group. In addition, significant relationships were revealed between severity of preoperative hydrocephalus and visual-spatial skills. The high percentage of children who needed special education reflects the severity of the impairments.

Conclusion

Despite the current opinion of a good quality of life after CPA treatment, careful long-term neurocognitive follow-up is needed in order to inform parents and teachers about the behavioral and cognitive sequelae and to contribute to timely social and educational intervention.

INTRODUCTION

In the last decade, anatomical, physiological and functional studies[1-3] confirm cerebellar involvement in cognitive functions. In consequence, the view on the cerebellum has widened to a modulator of cognitive and emotional processes.

Two examples of cerebellar neurobehavioral syndromes are the Posterior Fossa Syndrome[4] and the Cerebellar Cognitive Affective Syndrome (CCAS).[5] The Posterior Fossa Syndrome consists of transient short-term deficits, which begin one to six days postoperatively and gradually resolve over months. The most common feature is mutism and is often referred to as Mutism and Subsequent Dysarthria (MSD).[6] Other features are oropharyngeal dyspraxia, emotional lability, incontinence, and bizarre personality changes. CCAS has four major symptoms: disturbances of executive function, impaired spatial cognition, linguistic difficulties, and personality changes.

In children clusters of symptoms similar to CCAS[7,8] occur shortly after resection of a Cerebellar Pilocytic Astrocytoma (CPA), but long-term quality of life after CPA surgery seems favorable.[9,10] The follow-up of long-term sequelae of CPA surgery includes intellectual functioning, but not a systematic assessment of other cognitive functions.[10-12] Four studies report long-term cognitive impairment: attention in seven children,[11] executive in three out of four children,[13] difficulties with reading, spelling and working memory in one patient,[14] language, visual-spatial, or memory difficulties in three patients.[8]

Although behavioral problems related to the MSD syndrome are clinically recognizable, reports of long-term behavioral impairments related to CPA surgery are still scarce: persisting behavioral difficulties in one patient,[8] and passive, immature and childish behavior in another patient.[3] Parents describe demoralization, increased sensitivity and lower frustration tolerance. They experience the behavioral problems as more disabling than the concomitant cognitive impairments.[13]

The above-mentioned studies indicate that there are long-term cognitive and behavioral impairments after CPA treatment. Firm conclusions to their pattern or frequency cannot be drawn. Therefore the purpose of this study is to gain insight into long-term neurologic, neuropsychologic and behavioral sequelae in children after CPA treatment without additional chemo- or radiotherapy.

PATIENTS AND METHODS

Patients

Between 1993 and 2001 a consecutive series of twenty-six children were treated for CPA. Twenty-three patients (ten boys, thirteen girls) were included in this study. Inclusion criteria were no additional radio- or chemotherapy, age at surgery ≤ sixteen years, age at assessment ≥ six years (mean age twelve years nine months), interval surgery and assessment ≥ one year (mean interval three years and four months) and no deviant premorbid development as reported by parents and teachers. Patient characteristics are summarized in Table 1. Treatment for CPA consisted of tumor resection in all children and shunting of preoperative hydrocephalus in eleven children (48%). Nine children (39%) had a vermal incision, seven (30,5%) a surgical incision lateral of the vermis in the right hemisphere and seven (30,5%) in the left hemisphere. The tumor size ranged from two to seven cm.

Table 1 Patients Data

Pat	Age at testing (y.m)	Time surgery-testing (y.m)	Pre-operative hydrocephalus	Tumor site
1	10.3	5.3	Severe	Median, RH
2	16.3	3.0	Mild	Vermis
3	8.8	1.1	Absent	Sup. Vermis
4	14.0	1.9	Severe	Median, LH, RH
5	15.3	5.8	Severe	RH
6	21.6	5.3	Mild	Dorsal vermis
7	14.11	5.2	Mild	Median, LH, RH
8	22.11	5.5	Severe	Vermis, LH, RH, IVth ventricle
9	16.2	4.7	Severe	Vermis, LH, RH
10	12.3	1.10	Mild	Median, RH
11	10.2	1.7	Absent	Median, RH
12	14.0	6.0	Absent	RH
13	10.0	4.0	Severe	Median, RH, LH
14	14.5	8.10	Severe	LH
15	11.8	1.4	Absent	Vermis
16	6.7	2.8	Absent	Vermis, RH
17	11.6	6.0	Mild	Median, LH
18	6.7	2.6	Mild	Median, LH
19	11.8	1.4	Absent	Vermis
20	9.6	1.2	Absent	Vermis
21	13.11	1.9	Mild	LH
22	14.9	1.0	Severe	Median, RH, LH
23	6.10	1.0	Severe	Vermis, RH

Notes
Pat = patient, RH = right cerebellar hemisphere, LH = left cerebellar hemisphere, y=years, m=months

Methods

A child neurologist (C.C-B.) examined all children at the time of neuropsychologic assessment. Speech was assessed according to the "Mayo Clinic Lists"[15], in which speech characteristics such as voice quality, nasality, articulation, prosody and respiration are included.[16]

Pre- and postoperative brains MRI were studied to determine the preoperative maximum tumor diameter, site of the tumor and incision site. We computed the bicaudate index (BI) as a measure of ventricle dilatation at presentation.[17] We distinguished: no hydrocephalus (BI< 0.19), mild hydrocephalus (BI 0.19-0.26) and severe hydrocephalus (BI > 0.26).

Neuropsychologic tests developed for children and young adults were administered to assess skills in six domains:[18-22]

1. Nonverbal intelligence: Raven (Colored) Progressive Matrices (Raven CPM)
2. Memory: Rey Auditory-Verbal Learning Test (RAVLT), Delayed recall version of Rey Complex Figure Test (Rey CFT- delayed recall)
3. Language: Test for Reception of Grammar (TROG)
4. Visual-(spatial): Judgment of Line Orientation Test (JLOT), Facial Recognition Test (FRT), Line Bisection Test (LB) and copy version of Rey Complex Figure Test (Rey CFT-copy)
5. Executive skills: Trailmaking Test (TMT), Verbal Fluency, Wisconsin Modified Card Sorting Test (WMCST) and Wechsler Intelligence Scale for children-Revised Mazes (WISC-R Mazes)
6. Attention: Stroop Color-Word Test (Stroop) and Cancellation Test

All tests were administered in their Dutch versions. Manifest neuropsychologic deficits, spontaneous language and speech were judged by a child neuropsychologist (F.A.). Behavioral disturbances were evaluated from an observation of the child and interviews with the parents conform DSM IV criteria[23]. The results of observation and interview were discussed in a multidisciplinary team.

Statistics

The performances of the patients on the tests were compared with the normative data and converted into Z scores. The Z score reflects the extent a score deviates from the mean of a normal population. The χ^2 test was used to compare variance of our study group with the normal population and the Kolmogorov-Smirnov test was used to control for normal distribution. Differences between two or more groups were analyzed with the Mann-Whitney *U* test or the Kruskall-Wallis test. Data that did fulfill the requirements of parametric testing were analyzed with two-sided Students t test, and correlations were computed between continuous variables with a two-sided Pearson correlation matrix (SPSS 10.0/PC+).

RESULTS

Neurologic examination

The neurologic status at time of neuropsychologic assessment was normal to mildly impaired (see Table 2). Seven children had a mild ataxia (2, 6, 8, 16, 18, 22 and 23), one a mild nystagmus (7), and two a mild intention tremor of both hands (20, 21). One patient had had two generalized seizures (1) and two patients had visual field deficits due to optic atrophy (9, 22). An apraxic disorder in which oro-facial movements were more affected than limb movements was found in one child (16). Two children had upper limb neglect (3, 4).

Speech and Language

Dysarthria was present in five children (22%) (see Table 2). Deviant speech features were disturbances of vocal quality (2, 6, 8, 14), articulation problems (6, 8), slow speech rate (2, 16), voice tremor (16) and excess and equal stress (14). Seven children (30%) had language problems (Table 2) consisting of word finding difficulties (4, 21), non-fluent speech (17, 21), semantic-pragmatic problems (6, 8, 11) and phonological agraphia (12).

Neuropsychologic assessment

Table 3 shows the Z scores of the group (means and standard deviations), the p-values and the number of patients completing each test, as not all children were able to finish all tests. Three children were too young to complete the TMT, the Stroop, the Cancellation test and WMCST (16, 18, 23). Two patients were too old for the WISC-R Mazes (6, 8) and ten were too old for the TROG (2, 4, 5, 6, 7, 8, 9, 12, 14, 22). One child (3) could neither count nor read (Cancellation test, Stroop, TMT and WMCST) and two children became too tired to finish the complete test session (9, 10).

The scores on tests measuring sustained attention (Cancellation test; fluctuations: $p < 0.01$, speed: $p < 0.001$), executive functioning (WMCST; categories: $p < 0.05$, perseverations: $p < 0.05$), visual-spatial functions (LB; $p < 0.01$) and visual-spatial memory (Rey CFT-delayed recall: $p < 0.001$) showed weaker performances in comparison with the norms (Table 3).

Results of the Kruskall-Wallis test indicate that there were no significant differences in test results among the groups with a surgical incision in the vermis, left or right cerebellar hemisphere. Among the patients grouped according to extent of preoperative ventricle dilatation, Kruskall-Wallis test revealed a difference on the copy version of the Rey CFT ($p < 0.01$). The group with a severe hydrocephalus obtained a lower score on drawing a complex figure. A Pearson correlation matrix revealed no significant correlation between the duration of symptoms of increased intracranial pressure and test results. Significant correlations were found among maximum tumor diameter and visual-spatial skills (Rey

Table 2 Summary of results

Pat	Neurologic symptoms	Speech deficits	Language problems	Neuropsychologic impairments*	Behavioral problems	DSM IV diagnosis
1	Two seizures	ND	ND	Attention, visual(-spatial), executive and memory	Anxious	Overanxious Disorder of Childhood (300.02)
2	Mild ataxia	Speech rate, vocal quality (weak)	ND	Attention, visual(-spatial) and memory	Disinhibited	Alcohol Dependence (303.90)
3	Neglect of the right arm	ND	ND	Attention, visual(-spatial), executive and memory	Hypospontaneous and flattened affect	ND
4	Neglect of the left arm	ND	Word finding	Attention, visual(-spatial), executive and memory	Hypospontaneous and flattened affect	ND
5	ND	ND	ND	Executive and memory	ND	ND
6	Mild ataxia	Articulation, vocal quality (hoarse)	Semantic-pragmatic	Memory	Sticky and hyperspontaneous	ND
7	Mild nystagmus	ND	ND	Memory	ND	ND
8	Mild ataxia	Articulation, vocal quality (nasal)	Semantic-pragmatic	Attention, visual(-spatial), executive and memory	Hyperspontaneous	ND
9	Concentric visual field constriction	ND	ND	Attention, visual(-spatial) and memory	Hypospontaneous and flattened affect	ND
10	ND	ND	ND	Executive, visual(-spatial) and memory	Hypospontaneous and flattened affect	ND
11	ND	ND	Semantic-pragmatic	Attention, executive, and visual(-spatial)	Anxious and rigid	Asperger's disorder (299.80)
12	ND	ND	Phonological agraphia	Attention	ND	ND
13	ND	ND	ND	Attention, visual(-spatial) and memory	ND	ND
14	ND	Excess and equal stress, vocal quality (hoarse)	ND	Attention, visual(-spatial), executive and memory	ND	ND
15	ND	ND	ND	Attention	Anxious, nightmares	Posttraumatic stress disorder with delayed onset (309.81)
16	Mild ataxia, Apraxia,	Speech rate, voice tremor	ND	Visual(-spatial), executive and memory	ND	ND
17	ND	ND	Non-fluent	Executive	Anxious	Overanxious Disorder of Childhood (300.02)
18	Ataxia left leg	ND	ND	Attention and memory	Hypospontaneous and flattened affect	ND
19	ND	ND	ND	Attention	Posttraumatic stress	Posttraumatic stress disorder (309.81)
20	Intention-tremor	ND	ND	Attention and executive	Hyperactive	Attention-Deficit/ Hyperactivity Disorder, Combined Type (314.01)
21	Intention-tremor	ND	Non-fluent, word finding	Attention, visual(-spatial) and executive	ND	ND
22	Ataxia left	ND	ND	Attention, visual(-spatial) and executive	ND	ND
23	Ataxia left	ND	ND	Visual-(spatial)	Hypospontaneous and flattened affect	ND

ND = no dysfunction, * = an impairment is determined when the individual Z-score on the cognitive test is more than two standard deviations below the child's Z-score of intelligence.

Table 3 Neuropsychologic results grouped according to cognitive domain

Cognitive domain	Neuropsychologic tests	Z score (M ± SD)	P-value	N
Nonverbal intelligence	Raven CPM/PM	0.30 ± 1.00	NS	23
Language	TROG	0.16 ± 1.18	NS	13
Executive functions	TMT-A (speed)	-0.35 ± 1.19	NS	19
	TMT-B (speed)	-0.25 ± 1.29	NS	19
	WMCST (Categories)	-0.33 ± 1.32	**P < 0.05**	17
	WMCST (Perseverations)	-0.47 ± 0.51	**P < 0.05**	17
	Fluency	-0.16 ± 0.98	NS	22
	WISC-R Mazes	0.46 ± 1.19	NS	19
Visual(-spatial) functions	Rey CFT- copy	-0.17 ± 1.19	NS	23
	LB	-0.64 ± 1.49	**P < 0.01**	18
	FRT	0.10 ± 1.42	NS	20
	JLOT	-0.58 ± 1.61	NS	23
Attention	Cancellation test (Speed)	-2.06 ± 2.36	**P < 0.001**	19
	Cancellation test (Fluctuation)	-0.63 ± 0.60	**P < 0.01**	19
	Cancellation test (Accuracy)	0.21 ± 1.23	NS	19
	Stroop (Interference trial)	-0.17 ± 2.94	NS	19
Memory	RAVLT (Trails 1-5)	-0.07 ± 1.31	NS	23
	RAVLT - delayed recall	-0.04 ± 1.13	NS	23
	RCFT - delayed recall	-0.78 ± 0.85	**P < 0.001**	23

Notes
N = number of patients who completed the test, NS = not significant, CPM = Colored Progressive Matrices, PM = Progressive Matrices, TROG = Test for Reception of Grammar, TMT = Trailmaking Test, WMCST = Wisconsin Modified Card Sorting Test, WISC-R = Wechsler Intelligence Scale for Children Revised, CFT = Complex Figure Test, LB = Line Bisection Test, FRT = Facial Recognition Test, JLOT = Judgment of Line Orientation Test, RAVLT = Rey Auditory-Verbal Learning Test

CFT- copy: r = -0.46; JLOT: r= -0.49), mental speed (TMT A: r = -0.55), verbal long-term memory (RAVLT - delayed recall: r = -0.49), and executive functions (WMCST categories: r = -0.51). Also a significant correlation was found between maximum tumor diameter and ventricle dilatation (r = 0.69). In addition a significant correlation was revealed between sustained attention (Cancellation test) and time between surgery and assessment (r = 0,52).

In a normal population 2.3% of children have Z scores ≤ -2. We consider it of clinical importance if the percentage of children obtaining a Z score exceeds 2.3%. Analysis of the summary scores showed a Z score ≤ -2 in six children (26%) in the domain of attention, in five children (22%) in visual-spatial skills, in four children (17%) in executive functions, and in two children (8%) in verbal memory. Six of the above mentioned patients showed severe impairments (SD < -3) in distinct cognitive domains: attention (1, 14, 22), visual-spatial (1, 23), executive (1, 14), and non-verbal memory (10, 14, 18). The high percentage of children (24%), who needed special education, reflects the severity of the impairments.

Behavior

In fifteen children (65%) behavioral disturbances were observed, which could not all be classified according to the DSM IV [See Table 2]. The DSM-IV diagnoses were overanxious disorder of childhood (1, 17), alcohol abuse (2), Asperger's disorder (11), attention deficit/hyperactivity disorder (20), posttraumatic stress disorder with delayed onset (15) and without delayed onset (19). In addition we observed flattened affect (3, 4, 18, 23), disinhibited (2), clingy behavior (6), and verbal hyperspontaneous, logorrheic behavior (6, 8). In contrast we observed six children (3, 4, 9,10, 18, 23) with normal language comprehension but who did not speak spontaneously. They only spoke when directly addressed using normal syntax and a normal rate of speaking. The hypospontaneous behavior persisted in time and situation.

Summary of results

Long-term sequelae in the investigated domains were found in all children after CPA treatment. Apraxia, motor neglect, dysarthric features, language disturbances of various kind, disorders of sustained attention, visual-spatial impairments, executive difficulties, memory problems as well as behavioral problems were observed in various combinations and to different degrees. It should be emphasized that in this group of patients no clear-cut pattern of neurocognitive impairments could be systematically discerned. In addition a significant relationship was found between poor visuospatial skills and the severity, but not the duration of the preoperative hydrocephalus.

DISCUSSION

A CPA is a supposedly benign brain tumor with a good long-term quality of life.[9,10] In contrast with this optimistic view we found long-term neurocognitive disturbances in children after CPA treatment and a high percentage of children who needed special education (24%) compared to a national average of 5% in the Netherlands.[24]

Five children had a mild dysarthria at follow-up and two of them (patients 8 and 16) had suffered from MSD syndrome in the immediate postoperative phase. Usually the dysarthric component of MSD syndrome has a favorable prognosis.[6,17,25] The observation of long-term persisting dysarthria in our patients is in agreement with earlier findings[26] and shows that dysarthria after MSD can occasionally persist. Different types of dysarthria have been related to the presumed underlying pathophysiological mechanism of the corresponding neurologic disorder.[15] In ataxic dysarthria, deviant speech dimensions listed in order of decreasing severity are imprecise consonant production, excess and equal stress, irregular articulatory breakdown as well as harsh voice quality. In our study, disturbances of vocal quality and articulation were frequent dysarthric features. In none of the patients the two most specific

features of ataxic speech i.e. irregular articulatory breakdown and excess and equal stress occurred together. The literature suggests that cerebellar dysarthria mainly occurs in conjunction with a superior paravermal lesion.[27-29] We could not confirm this assumption as in the present study only one out of five dysarthric patients had such a lesion. We conclude that the observed speech features do not fit into any cluster of deviant speech dimensions.[15]

Seven children had language problems at follow-up. Three of them showed semantic-pragmatic difficulties: in one child the language deficit fitted in an Asperger's disorder,[30,31] and in two children the phenomenon of "cocktail party speech", also described in a subgroup of children with spina bifida and hydrocephalus,[32] seems adequate to describe the type of language disorder. In only one of the seven children the persisting language impairment (word finding difficulties) first occurred in the acute postoperative phase, but did not fit the syndrome of Mutism and Subsequent Language disorder (MSL).[7,33,34] Surprisingly we recorded the remaining language disturbances in the course of the later postoperative phase. It has been suggested that new long-term impairments could result from changes during the further postnatal development of the cerebellum,[3,14] leading to disruption in pathways that fail to develop properly as a result of the lesion. Thus delayed language difficulties in our patients might result from a growing into deficit.

We did not systematically assess naming, repetition, reading, and writing, but the description of long-term language characteristics of three children with MSL[7] suggests that standard language tests are not sensitive enough to detect sub clinical language impairments in children with a cerebellar lesion.

The occurrence of apraxia or neglect as described in our cerebellar patients is rare, but concomitant with two earlier reports in patients with cerebellar lesions.[5,35] Neuropsychologic assessment in our CPA children further revealed disorders of sustained attention, visual-spatial impairments, executive difficulties and memory problems. The improvement over time in sustained attention we found in our study, and the lower mean Z score in cognitive test results in a short-term postoperative study in a similar group,[7] suggest that neuropsychologic disturbances improve, but do not recover completely.

Our findings also demonstrate that severity but not duration of preoperative hydrocephalus is associated with lower visual-spatial performances. This implies that cognitive sequelae are not exclusively resulting from the cerebellar tumor and the surgical lesion, but that raised intracranial pressure plays an additional role, and, thus, might have a prognostic significance. As pre-operative neuropsychologic data are not available, it is impossible to determine exactly the weight of pre-operative (hydrocephalus and tumor) and postoperative factors (surgical lesions) on long-term neuropsychologic functioning. However a poor postoperative condition seems to be of prognostic importance, as relationships were found between the

occurrence of MSD or severe postoperative ataxia and disorders of attention at long-term follow-up.

Crossed cerebro-cerebellar connections are important in modulation of executive processes, temporal ordening and timing, attentional mechanisms, visual-spatial processing, memory and learning.[3] Our findings do not unequivocally support the concept of cerebellar lateralization of cognitive functions.[14,36] Only three out of fourteen children with an incision site in the right or left cerebellar hemisphere showed a pattern of impairments compatible with a crossed cerebro-cerebellar organization of cognitive functions. A possible explanation is that in case of a very large cerebellar hemisphere astrocytoma the neurosurgical procedure causes diaschisis extending to both cerebral hemispheres. SPECT scan findings in one child with both right parieto-occipital and left occipital hypoperfusion after left cerebellar hemispheric astrocytoma surgery support this assumption.[37] Another possibility could be that in children, lateralization of cerebro-cerebellar pathways might not as yet be completed.[38] Also crossed cerebellar diaschisis of glucose metabolism is not as prominent in children as in adults.[39]

Transient disturbances of affect regulation in the period immediately after cerebellar surgery are well-known.[6,17,25,33,34,40,41] Descriptions of long-term behavioral disturbances [8,13] are rare in childhood and hypospontaneity has previously been described as "a severe lack of spontaneity" whereby the children "tended to speak very little even after being encouraged to do so",[7] and "terse responses, lack of elaboration, reluctance to engage in conversation, long response latencies, and word-finding difficulties".[8] In contrast we frequently observed long-term behavioral disturbances with hypospontaneous behavior as a relatively common disorder. The hypospontaneous behavior we met in this study resembles one subtype of frontal dynamic aphasia.[42,43] It has been shown that this aphasic syndrome in fact encompasses three distinct neurolinguistic conditions, of which the third corresponds with verbal aspontaneity due to a frontal lesion.[44] In this condition, the lack of verbal drive may be part of a general akinesia and abulia, but differs from akinetic mutism because of absence of catatonia and incontinence. In our study 15 out of 19 children with a median or vermal tumor site displayed problems with affect regulation, whereas none of the four children with a hemispheric tumor location did. Affect modulation might be impaired, because of dysfunction of the cerebellar-cerebro circuitry connecting the cerebellum with the prefrontal cortex.[45-48] A example is the above-mentioned frontal-like (verbal) hypospontaneity in six of our patients with a vermal or median tumor site.[42-44]

The concept of CCAS has been introduced in a study of adult patients with cerebellar lesions of mixed etiologies.[5] However none of them presented with all four core-features of the syndrome at the same time. In another study in adults with a unilateral cerebellar stroke matched with controls for age, sex and educational levels, patients did also not fulfill all

criteria of CCAS.[49] The present study and earlier studies recorded in children with cerebellar damage due to surgery, chemo- or radiotherapy varying combinations of symptoms belonging to CCAS, but failed to identify all four symptoms in one subject.[7,8, 50, 51] As a syndrome is defined as a set of symptoms that occur together with sufficient frequency,[52] we conclude that although long-term cognitive disturbances definitely occur in children after CPA treatment, the ''Cerebellar Cognitive Affective Syndrome'' in children constitutes a rather loose complex of symptoms with variable composition.

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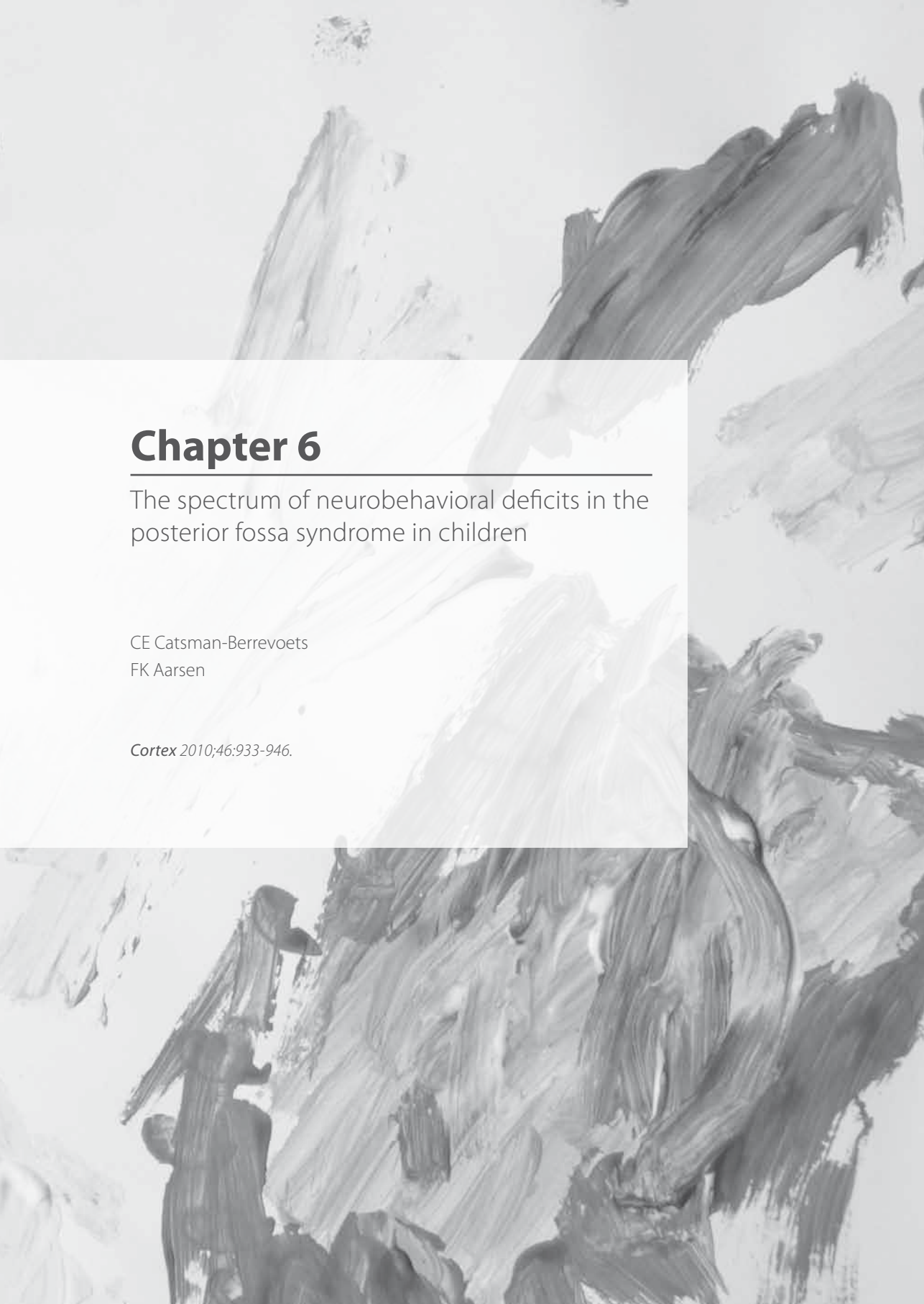

Chapter 6

The spectrum of neurobehavioral deficits in the posterior fossa syndrome in children

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ABSTRACT

Objective

The Posterior Fossa Syndrome (PFS) may occur in children after resection of cerebellar tumors. The most common feature is mutism, but also oropharyngeal dyspraxia, emotional lability and neuropsychiatric symptoms occur. We analyzed the spectrum of behavioral abnormalities, speech and language characteristics during PFS.

Methods

In order to identify PFS, all children with a cerebellar tumor admitted to our centre in the study period were prospectively assessed before and after tumor surgery. In the case of PFS, children were systematically followed by means of a standard protocol that included a daily neurologic examination and assessment of speech behavior. Speech was recorded on videotape before and immediately after surgery, and in cases of PFS at as short possible intervals for 4 weeks and subsequently every second week until the recurrence of speech and normalization of behavior. Data regarding clinical and behavioral features, duration of symptoms and mode of recovery were collected. Pre- and postoperative MRI data were studied. In 13 children with and two children without PFS SPECT scan could be performed.

Results

PFS occurred in 41 of 148 children. During recovery all children were dysarthric, but only in a few speech features specific for cerebellar dysarthria occurred. A significant correlation was found between duration of mutism and severity of neurologic symptoms. Significant correlations were also found between duration of mutism and abnormalities on SPECT scans of the left temporal lobe, the left and right basal nuclei, and the right frontal lobe.

Conclusions

In this study, impairments of higher cognitive functions were observed in the context of PFS. They varied in severity and composition between children with symptoms fitting into the spectrum of the Cerebellar Cognitive Affective Syndrome. SPECT scan findings suggest that these impairments are secondary to supratentorial metabolic hypofunction following cerebellar surgery.

INTRODUCTION

Acquired neurologic childhood mutism may be caused by damage to different brain regions in the context of various etiologies. Akinetic mutism in children has been described after hemorrhages in the left fronto-parietal area and the right insula,[1] in the acute stage of aphasia after left frontorolandic lesions, [2] in the course of acquired aphasia with seizure disorder; Landau Kleffner syndrome,[3] as well as in the context of an akinetic rigid syndrome in acquired parkinsonism.[4]

A unique syndrome characterized by Mutism and Subsequent Dysarthria (MSD) and associated neuropsychiatric symptoms may occur in children after resection of large midline cerebellar tumors. The first anecdotal reports date from the early seventies. [5-7] In some children, the loss of speech is associated with nuclear or supranuclear cranial nerve palsies and long tract signs, suggesting a bulbar or pseudobulbar palsy as the cause of the speech disturbance. [8-13] Because the absence of these symptoms in their patients suggested a cerebellar origin of the mutism, Rekate et al.[14] subsequently introduced the term 'cerebellar mutism'. The transient nature of the mutism and the dysarthria in the recovery period was the reason that this complex of symptoms was later renamed as the syndrome of cerebellar MSD.[15] These authors describe the core features of this syndrome as: 1) mutism after resection of a cerebellar mass lesion; 2) delayed onset of mutism after a brief interval of 1–2 days of relatively normal speech post surgery; 3) transient mutism that lasts from 1 day to 6 months followed by a severe dysarthria, which recovers completely in 1–3 months; 4) frequent association with other neurologic manifestations such as long tract signs and neurobehavioral abnormalities.[15-18] To date 283 patients with MSD syndrome have been described in detail.[19] A vast majority of these children display evident dysarthric features after the period of mutism, such as slow speech rate, monotonous, and ataxic speech.[19] In the phase of speech recovery, language disturbances, such as word finding difficulties,[20] agrammatism,[13,21] adynamic language, characterized by a lack of verbal initiative,[13,22,23] comprehension deficits,[20] and reading or writing problems[22,24] also have been found. Extension of the spectrum of MSD syndrome with symptoms such as emotional lability, poor oral intake, decreased spontaneous initiation of movements, impaired eye opening, and urinary retention lead to the introduction of the broader term Posterior Fossa Syndrome (PFS).[25,26] In subsequent papers, also depressed affect,[27] agitation,[27] apathy[13] and transient cortical blindness[28,29] were described. Different combinations of these symptoms with varying severity occur in the majority of PFS patients. However, MSD is not always the key feature of PFS.[23, 30]

Although 93% of PFS patients have been described after cerebellar tumor surgery[31] the syndrome may also develop shortly after traumatic, vascular or infectious events of the cerebellum.[31,32] Frim and Ogilvy[33] report MSD syndrome in a child after resection of a cavernous

malformation of the right pons at the level of the medial cerebellar peduncle. Patients with PFS syndrome have generally, but not exclusively, been young, and for this reason PFS is considered to be a childhood syndrome.[34] The incomplete development of speech motor control and language in children has been suggested as an important reason for the predilection of PFS for the young age group.[35]

The pathophysiology and anatomic basis of PFS are poorly understood and postoperative Magnetic Resonance Imaging (MRI) imaging has failed to reveal either a definite anatomical substrate or mechanism of injury.[25,33,36-40] Previous studies have suggested a variety of underlying mechanisms for PFS, such as postoperative spasm of vessels supplying the cerebellum and brainstem,[12,39] a transient dysfunction of the A9 and A10 dopaminergic cell-group in the mesencephalon[16,41] or perturbation of the dentato-thalamo-cortical pathways, resulting in a diminished or altered function of supratentorial brain structures.[17,37,39,42-44] 99mTc-hexamethylpropyleneamine oxime-Single Photon Emission Computed Tomography (SPECT) scan studies in children with postoperative mutism have previously revealed abnormal supratentorial perfusion patterns reflecting a reduced metabolic demand.[42-46] However, the number of reported patients was small, findings were inconsistent, and the correlation of SPECT scan findings with components of PFS other than cerebellar mutism is not well known.

In the present study, we report on a cohort of 41 children with PFS after cerebellar tumor surgery who were prospectively followed in our hospital. Our objectives were: 1) to analyze the clinical features of PFS and especially the spectrum of behavioral abnormalities during PFS, 2) to determine speech and language characteristics in the context of PFS and 3) to gain an understanding of the pathophysiology of PFS by attaining semi-quantitative visualization of the perfusion of different brain areas after cerebellar tumor surgery by means of postoperative SPECT scans.

PATIENTS AND METHODS

Patients

All children admitted between 1989 and 2007 to the Erasmus Medical Centre/Sophia Children's Hospital for cerebellar tumor resection were prospectively assessed according to a standard follow-up protocol, in order to identify those children developing PFS. The upper age limit to be included in this study was set at 17 years 11 months, following the age range for children and youth of the World Health Organization.

Methods

Assessment included a daily neurologic examination and assessment of speech behavior (in very young children elicited by, and in response to their parents) in the first 2 weeks after surgery, that is, until the risk of developing PFS symptoms became almost zero. Speech behavior was recorded on videotape before and immediately after surgery, and in cases of PFS at as short possible intervals for 4 weeks. Subsequently, these patients were assessed every 2nd week until the recurrence of speech or normalization of behavior. Behavioral abnormalities were classified after observation of the child and interviews with the parents according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criteria.[47] Speech (spontaneous language, repetition of phonemes and sentences, and – if possible – reading aloud) was assessed using the Mayo Clinic List,[48] in which speech characteristics such as voice quality, nasality, articulation, speech rate and respiration are included. Language was evaluated within the context of the neurologic examination and special attention was paid to clinical evaluation of praxis, language comprehension, verbal perseverations, occurrence of syntactic errors or word finding problems.

At onset of PFS, a brain MRI was performed in order to exclude postoperative complications such as an intracerebral or subdural hematoma as cause of the PFS. Also cerebral or meningeal infections were excluded by spinal fluid investigations. Pre- and postoperative brain MRI scans were studied to determine tumor site and preoperative maximum tumor diameter. We computed the bicaudate index (BI) as a measure of ventricle dilatation at presentation and at onset of PFS.[17] We categorized ventricular diameter as no hydrocephalus (BI < .19), mild hydrocephalus (BI .19–.26) or severe hydrocephalus (BI > .26). Perfusion of different brain areas was visualized semi quantitatively by means of postoperative SPECT scans. A limitation was that these scans could only be performed in the children, who could be submitted to this scan without anesthesia. The following eight brain regions were studied in transversal, coronal and sagittal brain images; brainstem, cerebellum, thalamus, basal nuclei and the frontal, parietal, temporal and occipital cortical regions. Regional cerebral blood flow values were normalized to the mean activity in a cerebellar reference slice from the normal data base of the hospital. In the regions of interest, the Z-scores were calculated for each region. Z-score >2.0 was considered mildly abnormal. Z-score >3.0 was considered severely abnormal. Perfusion patterns of all scans were reviewed by the same senior nuclear medicine specialist, who was unaware of the patient's clinical course and findings.

Statistics

Data were analyzed using the Mann–Whitney *U* test and Spearman rank correlations for categorical variables and with the Pearson correlation matrix for continuous variables (SPSS 16.0).

RESULTS

Patient characteristics

In the study period a cerebellar tumor was surgically removed in 148 children. Six children needed a second surgery because of a large residual tumor or tumor recurrence. Tumor types are presented in Table 1. Forty-one children (26.6%) developed PFS and could be included in the present study. Twenty-seven of these children were male and 14 were female.

Table 1 Pathological diagnoses of the cerebellar tumors in all 148 children (including surgery for recurrent tumor in six children) versus the children with PFS.

	Cerebellar tumor resections	Surgery of recurrent tumor	PFS	% of total number of cerebellar tumor surgery	% of tumor type
	N = 154	6 /154	N = 41	26.6	
Medulloblastoma	N = 65	2 / 65	N = 26	16.9	40
Pilocytic Astrocytoma	N = 62	4 / 62	N = 10	6.5	16.1
Ependymoma	N = 20		N = 4	2.6	20
Other diagnosis	N = 7		N = 1	0.6	14

Notes
Other diagnosis are Ganglioglioma N= 3, Atypical Teratoid Rhabdoid Tumor: N= 1, Germinoma :N= 1, Plexus Papilloma: N=1, Hemangioblastoma: N=1

Age at surgery varied from 1 year and 9 months to 17 years and 9 months (mean age 6 years and 4 months, standard deviation – SD 4 years and 2 months) and did not significantly differ from the mean age of the children that did not develop PFS symptoms (age range 1 year 3 months to 15 years 7 months, mean age 7 years and 1 month, SD 4 years and 5 months). Age distribution is represented in Fig 1.

PFS most frequently occurred after resection of medulloblastoma (40%). All tumors of children who developed PFS were located in the midline, occasionally extending into the left or right paravermal regions (see Table 2). Maximum tumor diameter ranged between 3.4 and 7.2 cm, with a mean of 5.2 cm. Preoperative hydrocephalus was absent in 14, mild in 16 and severe in 11 children. At onset of PFS, 28 children had no, 10 a mild and three children a severe hydrocephalus (see Table 2).

Clinical features of PFS

Delay before onset of symptoms varied from 0 to 5 days in 38 children (see Table 2). The 13 children with no apparent interval between surgery and PFS onset had been kept sedated on a ventilator for 1–2 days after surgery. Symptoms of PFS were noted after sedation was stopped and the tracheal tube was removed. In three children, PFS symptoms started 7, 9 and 11 days after surgery. Two of them (patients 25 and 41) developed infarctions in the territory

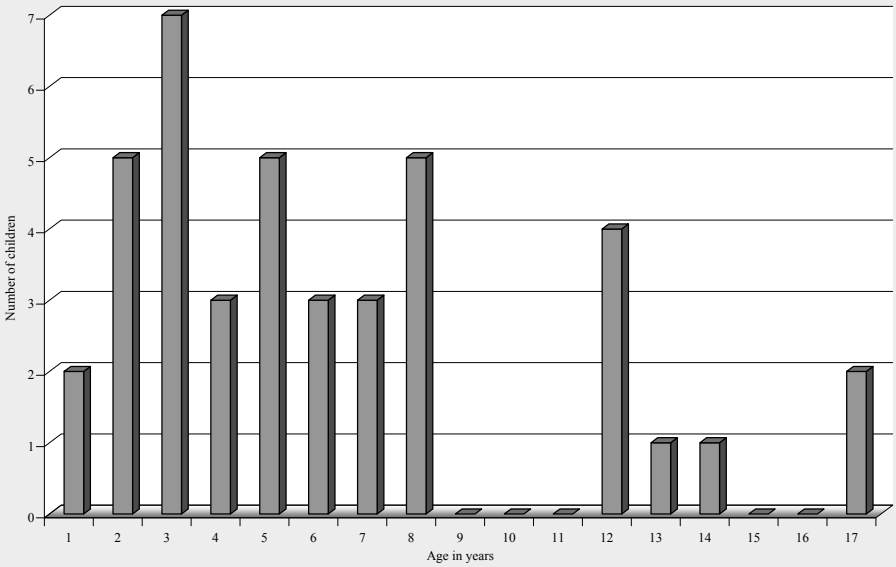

Figure 1 Age distribution of 41 children with MSD/PFS after cerebellar tumor surgery

of the middle cerebral artery in the course of PFS.[49] Duration of the acute PFS symptoms varied from 1 to 212 days. Two children (patients 40 and 41) died during PFS, 20 and 30 days after PFS onset respectively (see Table 2). Patient 40 died due to sepsis during a course of chemotherapy and patient 42 due to diffuse brain swelling after bilateral ischemic stroke in the territories of the middle cerebral arteries. At onset of PFS, all children had new or worsening neurologic symptoms such as ataxia, pyramidal paresis, or oculomotor dysfunction to varying degrees. Characteristically, they all had a diminished facial expression. All previously toilet trained children temporarily lost bladder and bowel control. Mutism developed in 36 children (88%), irritability in 34 (83%), whining in 29 (70%) and severe apathy in 29 (70%) (see Table 3). In addition to these symptoms, a wide spectrum of other behavioral abnormalities was observed (see Table 3). Fourteen children (34%) showed autistic behavior and avoided social and physical contact with their parents and caregivers. In patients 31 and 34 transient cerebellar eye closure was observed and in patients 31 and 35, transient cortical blindness occurred.

Patient 39 went through a 10-day period of transient compulsive pre-sleep behavior.[50,51] Aggressive behavior was observed in patient 18 and a transient period of forced crying and laughing with motor perseverations occurred in patients 33 and 38. In the 5 children with PFS and absent mutism (patients 4, 5, 33, 38, 41), speech production was severely reduced and limited to single words or short sentences which could only be elicited after vigorous stimulation. In one of the latter children, (patient 33) word finding difficulties were present.

Table 2 Summary of clinical characteristics of children with Posterior Fossa Syndrome after cerebellar tumor surgery

Patient number	Gender	Age y.m	Tumor type	Tumor site	MTD (cm)	BI		Delay before PFS (days)	Duration PFS (days)
						Preop	Postop		
1	M	7.6	PA	vermis	4.0	0.21	0.12	3	1
2[a]	F	3.10	AII	midline	5.5	0.40	0.2	3	3
3	M	6.11	MB	vermis	4.5	0.23	0.19	1	5
4[a]	M	2.6	AII	vermis	7.2	0.19	0.25	2	6
5[a]	M	3.9	MB	vermis	3.5	0.09	0.13	4	6
6	M	8.8	MB	vermis	4.8	0,18	0.11	0	7
7	F	3.0	MB	vermis	5.7	0.30	0.26	2	7
8	F	7.11	MB	vermis	5.7	0.28	0.15	0	9
9	M	5.1	EII	vermis	4.5	0.18	0.43	9	11
10	F	1.9	PA	midline/RH	4.4	0.21	0.11	2	12
11	M	2.3	E	midline/RH	5.2	0.17	0.18	3	14
12	M	4.1	MB	vermis	5.0	0.22	0.19	2	14
13	M	5.2	MB	vermis	4.2	0.15	0.19	1	15
14	M	8.11	MB	vermis	4,6	0.17	0.17	3	15
15	M	17.6	PA	vermis	5.2	0.29	0.14	1	16
16	F	7.1	MB	vermis	3.8	0.22	0.05	0	20
17	F	4.9	MB	vermis	4.8	0.24	0.19	0	21
18	M	3.7	MB	vermis	6.0	0.13	0.28	0	24
19	F	5.4	PA	midline/LH	4.8	0.24	0.10	0	25
20	M	12.3	MB	vermis	4.5	0.22	0.10	3	28
21	M	3.2	PA	midline	3.5	0.26	0.10	0	29
22	F	2.4	MB	vermis	6.0	0.10	0.14	5	30
23	F	8.10	MB	vermis /LH	4.7	0.23	0.05	0	32
24	F	2.1	MB	vermis	5.0	0.27	0.12	1	32
25	M	2.8	E	vermis	7.0	0.26	0.21	11	35
26	M	5.0	MB	vermis	5.0	0.32	0.10	1	36
27	M	4.0	PA	vermis /RH	4.2	0.11	0.11	3	37
28	M	6.9	MB	vermis	6.0	0.25	0.15	1	56
29	M	8.0	MB	vermis	5.0	0.29	0.12	1	60
30	F	8.3	MB	vermis	5.5	0.33	0.18	2	60
31	M	17.9	MB	vermis	4.3	0.25	0.11	1	70
32	F	5.8	PA	vermis	5.0	0.27	0.03	0	75
33[a]	M	13.4	PA	vermis	5.0	0.25	0.17	3	80
34	F	14.0	MB	vermis	4.0	0.12	0.14	4	86
35	M	3.0	MB	vermis	4.3	0.1	0.25	0	102
36	M	6.7	MB	vermis	4.9	0.15	0.13	0	124
37	M	12.0	MB	vermis	7.1	0.29	0.09	0	150
38[a]	M	12.7	PA	vermis	6.0	0.37	0.25	5	176
39	M	12.0	MB	vermis	4.1	0.19	0.14	3	212
40	M	3.3	MB	vermis	3.4	0.15	0.16	0	20 days[b]
41[a]	F	1.3	G	vermis /RH	3.5	0.16	0.28	7	30 days[b]

Notes y = years, m = months, MTD = maximal tumor diameter, cm = centimeter, BI = Bicaudate Index, Preop = preoperative, Postop = postoperative, M = male, F= female, PA = pilocytic astrocytoma, MB = medulloblastoma, E = ependymoma, G = germinoma, AII = astrocytoma grade II, LH = left cerebellar hemisphere, RH = right cerebellar hemisphere, a = PFS without mutism, b = died post surgery

Table 3 Summary of PFS characteristics

Patient number	Reduced speech	Mutism	Irritable	Whining	Apathy	Autism	Other symptoms
1		+					
2		+	+	+			
3		+	+				
4	+		+	+	+	+	
5#	+		+	+	+	+	
6		+	+	+			
7		+	+		+		
8		+	+	+	+		
9		+			+		strikingly good natured
10		+	+	+		+	
11		+	+	+		+	axial tremor
12		+	+	+	+	+	perioral dyskinesias
13		+					
14#		+	+	+	+		
15#		+			+		perioral dyskinesias
16#		+	+	+	+		
17		+	+	+			
18		+	+	+	+		aggressive
19		+	+	+	+	+	perioral dyskinesias
20#		+	+	+	+		cortical blindness
21		+	+	+	+	+	
22		+	+	+	+	+	
23		+	+	+	+		hypokinesia
24		+	+	+	+		
25		+	+	+	+	+	
26		+	+	+			
27#		+	+	+	+		hypokinesia
28		+	+	+	+	+	
29		+	+		+		
30		+			+		
31#		+			+		transient cerebellar eye closure, cortical blindness
32.		+					
33#	+		+		+	+	forced crying and laughing, perseverations, word finding problems, reduced language comprehension
34#		+	+	+	+		transient cerebellar eye closure
35#		+	+	+	+	+	cortical blindness, oral dyskinesias
36#		+	+	+			from 15 days after PFS onset strikingly good natured
37#		+	+	+	+		oral dyskinesias
38	+		+		+	+	forced crying and laughing, perseverations
39#		+	+	+	+	+	compulsive pre-sleep disorder, perseverations
40		+	+	+			
41	+		+	+			

Notes PFS = Posterior Fossa Syndrome, + = present, # = SPECT scan available, † = died before onset of recovery of PFS

In this boy, language comprehension was also reduced at clinical neurologic evaluation. An older age at time of PFS correlated significantly with a longer duration of PFS symptoms ($r = .46$, $p < .01$). No correlations were found between tumor size, severity of pre- or postoperative hydrocephalus, and the duration of PFS. In the course of PFS, the irritable behavior and whining as well as the severe apathy and facial expression gradually normalized in all children well before speech onset. In one child (patient 36) who was described as a boy who avoided social and physical contact before tumor diagnosis, the initial irritable PFS behavior changed after 20 days to the opposite. He became particularly good natured and communicative until speech onset 150 days after surgery, when once again his behavior gradually became anxious and rigid. At follow-up, he was diagnosed with Asperger syndrome. Only in one patient did behavioral disturbances and speech impairment disappear in the reverse order. In patient 39, recovery of speech occurred after 28 days of mutism but apathy and severely abnormal irritable and autistic behavior persisted for 7 months.

Speech features during recovery of PFS

In 40 children with PFS, speech was analyzed either during PFS in patients with reduced speech (patients 4, 5, 33, 38 and 41) or after speech onset in the children with mutism. Speech characteristics and/or behavior of patients 1, 9, 15, 20, 25, 26, 27, 28, 29, 30, 33, 34, 37, 38, and 41 of our cohort were described in more detail in earlier papers by our group.[1] The speech features that were heard in the children of our cohort are represented in Table 4. The most frequently occurring deviant speech feature was slow speech rate in 33 children. Thirteen of these 33 children spoke in grammatically correct but very short phrases, and had a severely reduced verbal output. The two most specific features of ataxic speech according to Darley et al. (1969),[48] excess and equal stress and irregular articulatory breakdown, were only present in patient 21. Four other patients (23, 27, 31, 35) had only one such feature; excess and equal stress. In patients 27 and 35, a prominent voice tremor was also present. In patient 30, alternating loudness was present, which is a specific feature of cerebellar speech according to Kluin et al. (1988).[52]

SPECT scan findings

Fifteen of the children with a cerebellar tumor could be examined with SPECT scan after tumor surgery. In 13 of the children with PFS, SPECT scans were performed at variable time points after surgery, but well within the period of PFS symptoms (see Table 5). In the two children without PFS (N1 and N2) who had a postoperative SPECT scan, a medulloblastoma was surgically removed. These tumors were both situated medially and in the vermis of the cerebellum and had a maximum diameter of 4 cm and 4.5 cm respectively. Postoperatively, these two children had a mild trunk and limb ataxia and patient N1 also had a left pyramidal paresis. Behavioral symptoms in both children were limited to a mild apathy of few days duration

Table 4 Speech features in the 40 children with Posterior Fossa Syndrome

Speech feature	Specific feature	Number of patients
Pitch	Low pitch	3
	High pitch	3
	Pitch breaks	1
Loudness	Monoloudness [a]	5
	Alternating loudness#	1
	Hypophonia	10
Vocal quality	Harsh voice [a]	3
	Hoarse wet voice	2
	Strained voice	2
	Hypernasality	1
Respiration	Audible inspiration	4
Prosody	Slow rate [a]	33
	Short phrases	13
	Variable rate#	1
	Voice tremor	2
Articulation	Imprecise consonants	4
	Distorted vowels [a]	4
	Excess and equal stress [a] #	5
	Irregular articulatory breakdowns [a] #	1

Notes

[a] Characteristic features of ataxic dysarthria in adults according to Darley et al.1969, [#] Characteristic features of ataxic dysarthria in adults according to Kluin et al.1988

that was concordant with the period of discomfort and stress after surgery. Duration of the behavioral and speech abnormalities in the children with PFS as well as neurologic deficits and abnormal SPECT scan findings are represented in Table 5.

This table shows that in all children with PFS, a severe perfusion deficit was present at the resection site bilaterally in the centre of the cerebellum. In contrast in the children without PFS (N1 and N2) the perfusion deficit was unilateral in N1 and mild and bilateral in N2. Hypoperfusion of the brainstem was observed in all, but four children (N1, 33, 15 and 31). Hypoperfusion of frontal cortical regions was also present in most children. Only patient N1 did not show hypoperfusion in the right frontal region and in patient 14 no frontal cortical perfusion deficits were detected at all. Bilateral hypoperfusion in temporal and occipital areas occurred exclusively in children with PFS and more specifically, tended to be present in the children with PFS who had more severe neurologic symptoms. In patients 15, 20, 33 and 37, follow-up SPECT scans were also performed later during the PFS period. These scans showed less pronounced hypoperfusion in the above mentioned areas. In patient 37 a third SPECT scan was performed 2 years after surgery, showing a residual hypoperfusion deficit at the cerebellar surgery site and in contrast complete resolution of the supratentorial cortical abnormalities (see Fig 2). No correlations were found between the severity or the location of

Table 5 Neurological and SPECT scan findings in patients with Posterior Fossa Syndrome, with and without mutism

Pat	Gender Age (y.m)	Duration (days)		Cerebellar signs	Pyr tract	^{99m}Tc-HMPAO SPECT scan findings representing R/L diffusion pattern								
		Beh	Mutism	Trunk Limbs Ocular	Left Right	dps	BS	Cer	Thal	BN	Front	Par	Temp	Occ
					Normal									
N1	M (9.6)			+ + n	+ n	6	-	n/ --	n/n	n/n	-/n	--/n	-/n	-/n
N2	M (7.3)			+ + n	n n	22	n	-/-	n/n	n/n	-/-	n/n	n/n	n/n
	PFS, no Mutism													
33	M (13.4)	80		n + n	n +	24	n	--/-	n/n	n/n	-/-	n/n	n/n	n/n
5	M (3.9)	12		N + +	n n	9	-	-/--	--/-	--/-	--/--	n/n	--/--	-/-
					PFS and Mutism									
14	M (8.11)	10	15	++ +L n	n n	14	-	--/--	n/n	n/n	N/n	-/ -	n/n	n/n
39	M (12.0)	212	28	++ + +	n n	38	-	--/--	--/--	n/n	--/--	n/n	n/n	--/--
36	M (6.7)	20	124	+ ++R n	++ n	80	-	-/--	n/n	n/n	--/-	n/n	n/-	n/-
15	M (17.6)	3	16	++ + +	n +	13	n	--/-	n/n	n/n	-/-	n/n	-/-	-/-
16	F (7.1)	15	20	++ + +	+ n	11	-	--/--	-/-	n/n	-/-	n/n	-/-	-/-
27	M (4.0)	20	31	++ + +	+ n	11	--	--/--	-/n	n/n	-/-	n/n	-/-	-/-
20	M (12.3)	20	28	++ ++ ++	++ ++	7	-	--/--	n/n	n/n	--/--	n/n	-/-	-/-
31	M (17.9)	45	70	++ ++ ++	++ ++	26	n	--/--	n/-	n/n	--/--	n/n	-/-	-/-
34	F (14.7)	50	86	++ ++ ++	+ +	11	-	--/--	-/-	-/-	--/--	n/n	-/-	-/-
35	M (3.0)	80	102	++ ++ ++	++ ++	74	--	--/-	--/--	-/-	--/--	n/n	-/-	--/--
37	M (12.0)	95	150	++ ++ ++	++ ++	24	-	--/--	-/-	-/-	--/--	n/n	--/--	-/-

Notes Pat = patient number, PFS = posterior fossa syndrome, N= child without symptoms of PFS after cerebellar tumor surgery, Pyr = pyramidal, Beh = behavior, dps = days postsurgery, n = normal, L= left, R = right, + = moderately, ++ = severe, - = moderate deficit, -- = severe deficit, VI = abducens nerve, VII = facial nerve, BS = brainstem, Cer = cerebellum, Thal = thalamus, BN = basal nuclei, Front = frontal cortex, Par = parietal cortex, Temp = temporal cortex, Occ = occipital cortex, y.m = years.months, F = female, M = male

SPECT scan abnormalities and the total duration of speech and behavioral symptoms within the spectrum of the PFS. Significant correlations were found, when only duration of mutism was considered as variable. Significant correlations were found between duration of mutism and severity of neurologic symptoms ($r = .69$, $p = .02$), severity of SPECT scan abnormalities of the left temporal lobe ($r = .67$, $p = .03$), the left and right basal nuclei (both $r = .65$, $p = .03$) and the right frontal lobe ($r = .80$, $p = .003$).

DISCUSSION

Incidence and risk factors

The incidence of PFS in our study is in agreement with the 24% found in the large prospective study of children with medulloblastoma of the Children's Cancer Group (CCG).[53] It also falls within the range of incidences found in retrospective studies which varied between 8% and 31%.[19] In the multicentre CCG study, 107 children with postoperative cerebellar mutism were

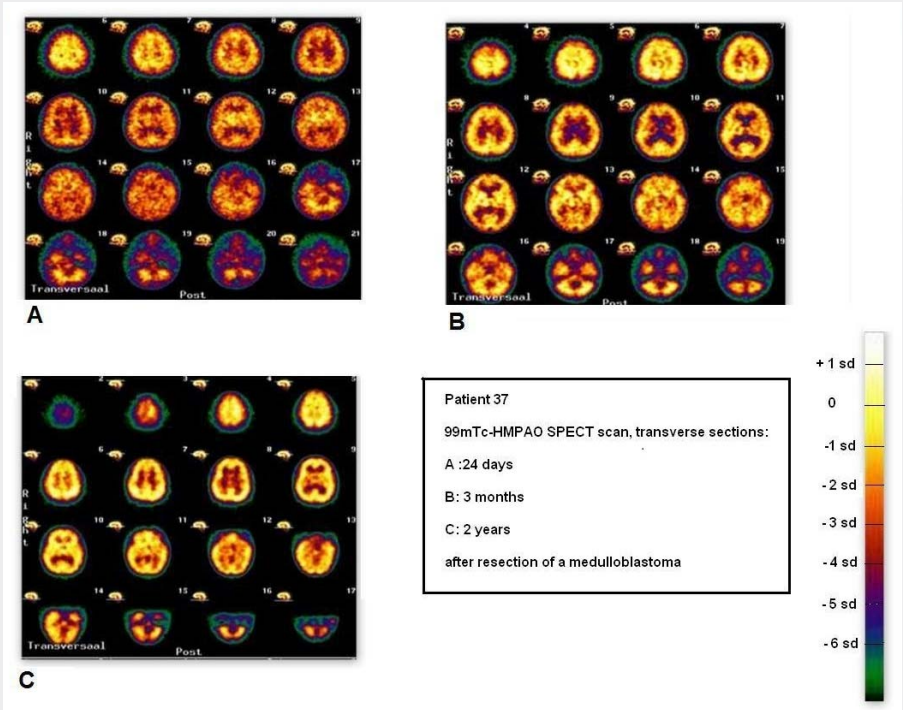

Figure 2 ^{99m}Tc-HMPAO SPECT scan findings in patient 37 at 24 days, at 3 months, and 2 years after resection of a medulloblastoma

identified. A research assistant collected the information on PFS in a short standard survey questionnaire, after consultation with the neurosurgeon and/or attending neurologist. Duration of mutism, irritability, ataxia and pareses were scored on a semi quantitative severity scale, but detailed characteristics of PFS in these children were not collected and no detailed psychometric or language testing was performed. We therefore present the largest cohort of children with PFS after cerebellar tumor surgery prospectively studied in more or greater detail.

Several risk factors for the development of PFS have been proposed. An interaction was previously found between type and size of lesion, such that a child with medulloblastoma and a maximum tumor diameter exceeding 5 cm has a high risk to develop postsurgical MSD.[17] In the present study, 64% of children with PFS had a medulloblastoma, but in only 43% of these children did the maximum tumor diameter exceed 5 cm. From this we conclude, that other risk factors also play an important role in the development of PFS. Additional risk factors for development of PFS that were identified in earlier studies are midline location of the tumor,[25] tumor localization adjacent to the IVth ventricle[15] and length of vermis incision.[38]

Robertsen et al. (2006)[53] found no correlation between postsurgical occurrence of PFS syndrome and tumor location in the vermis in their study of 450 children with medulloblastoma. Their attention on the cerebellar vermis as critical in the pathogenesis of PFS was likely caused by observations of a possible relationship between neurobehavioral abnormalities in children and developmental abnormalities of the cerebellum. In children with attention deficit hyperactivity disorder and in children with fragile X syndrome, smaller posterior lobes of the vermis are found in quantitative morphometry studies.[54-56] In addition in children with developmental malformations of the vermis, affective and social disorders associated with autistic symptoms have been reported.[57]
Kellogg and Piatt (1997)[40] introduced a paravermal surgical approach, in order to prevent vermal damage in children with cerebellar tumors. However, PFS continued to occur despite this change in practice that avoided the splitting of the vermis.[13] Consequently, vermal location and surgical damage to the vermis cannot be the key determinants in the development of PFS. Richter et al. (2005)[58] suggested that, although further data in the human literature are lacking, disruption of fluency of speech in children with MSD in the context of PFS may be caused by lesions of the deep cerebellar nuclei, more specifically the interposed nuclei and parts of dentate nuclei.

Clinical features of PFS

Thirteen of our patients (42%) did not speak before PFS onset. However, this observation likely reflects the current clinical practice in our hospital to keep children sedated and on a ventilator for one or two days after surgery, in order to control and stabilize the clinical condition of the child in the controlled environment of an intensive care unit.

The spectrum of symptoms of PFS in the children in this study varied from transient mutism without neurobehavioral symptoms in two patients, to mutism and severe behavioral symptoms of longer duration in the majority of children (83%). In 5 patients (12%), characteristic behavioral PFS symptoms were associated with a severe reduction in spontaneous speech, which never progressed to mutism. Previous studies in children and adults clearly indicate that the cerebellum is involved in a broad spectrum of linguistic functions, such as verbal fluency, word retrieval, syntax, reading, writing and meta linguistic abilities.[21,43] Clinical neurologic assessment of our patients did not reveal language comprehension deficits. However, language was not extensively evaluated by detailed linguistic analysis and therefore a linguistic disorder causing this speech reduction cannot be completely excluded.

In all but one child, behavioral symptoms faded before onset or normalization of speech. In this boy (patient 39), speech gradually had normalized long before amelioration of the particularly severe behavioral and emotional deficits. This reversed pattern of diminishing of PFS symptoms may have been associated with his pre-morbid behavior. Before tumor diagnosis,

his parents had noticed that he avoided social and physical contact and suspected an autism spectrum disorder. Eventually, this child was diagnosed with pervasive developmental disorder, not otherwise specified.

Although mutism is considered the key symptom of PFS, occasionally dissociation of speech and behavioral symptoms or affective disturbances are documented as the sole consequence of cerebellar surgery.[21,23] Systematic cognitive and behavioral assessments in children who do develop PFS symptoms but not mutism after cerebellar surgery have not been published previously. It seems plausible that cognitive deficits in children, manifesting only a partial PFS go unnoticed. Recognition of children exclusively demonstrating symptoms in the behavioral spectrum of PFS syndrome is important, because behavioral problems may persist in the long-term. Timely recognition and interventions are strongly advocated. [21,22]

The neurobehavioral symptoms in the children in our study agree with those described previously. They include irritable behavior, whining and inconsolable crying, severe apathy and autistic behavior, transient cortical blindness, forced crying and laughing, and transient cerebellar eye closure. [13,25-30,59] In one patient, compulsive pre-sleep behavior was observed, which as yet has not been described in the context of PFS or other cerebellar disease.[51] Compulsive pre-sleep behavior is a disorder of vigilance characterized by the following behavioral abnormalities: patients are apragmatic, abulic, remain immobile or supine for long periods of time in a posture mimicking sleep with their eyes closed. Compulsive pre-sleep behavior has been described after bilateral lesions of the paramedian thalamic nuclei[50,60,61] Guilleminault et al. (1993) classified this state as 'waking' because the patients exhibited a slowed a rhythm on Electroencephalogram (EEG) recordings and were able to react rapidly to slight stimulation and called this period 'dearousal'. During this abnormal waking, a reduction in frontal, cingular and anterior metabolism has been observed using positron emission tomography. [62]

All children in our study had articulation impairments during recovery of mutism. However, also the five children with severe reduction of spontaneous speech during PFS had articulation problems, which only slowly subsided in the course of normalization of speech production. This observation emphasizes that PFS without mutism, but with reduced speech utterances is part of the continuum of speech disturbances within the PFS spectrum. Slow speech rate was the most frequently encountered speech feature in our patients, followed by hypophonia and the production of short phrases. These deviant speech features are however not specific for cerebellar 'ataxic' dysarthria.[48,58,63] The most characteristic features of cerebellar 'ataxic' dysarthria, which are excess and equal stress and irregular articulatory breakdown, were rarely present. One single cerebellar speech feature occurred in four children and both characteristic features only in one child.

Based on our prior observation in five children, we suggested in our initial description of the core features of MSD that dysarthria completely recovers in 1–3 months. [15] However, other studies on long-term sequelae after cerebellar tumor surgery have described an incomplete recovery of speech production. [22,64] Huber et al. (2006) described persistent motor speech deficits in a systematic long-term study in children with MSD more than 5 years after cerebellar tumor surgery. Until now, only one child was described who did not recover from PFS and was still mute and showed agitated tearful behavior 2.5 years after cerebellar surgery.[65]

There are two proposed explanations for the development of MSD in the context of PFS: the anarthria hypothesis and the hypothesis of impaired higher speech functions.[58] The anarthria hypothesis considers MSD as the most severe form of dysarthria. On the basis of studies in adults with cerebellar stroke and supported by functional MRI (fMRI) findings, the cerebellar regions crucial for the development of cerebellar ataxic speech are thought to be situated in the paravermal regions on either side in the superior cerebellum, corresponding with paravermal lobules VI and VII. [58,66,67] In our patients, surgical lesions were limited to the cerebellar midline and occasionally extended into the left or right paravermal region. In the boy who had both characteristic ataxic speech features, the surgical lesion did not extend into both paravermal areas. For these reasons, our findings do not support the anarthria hypothesis.

The hypothesis of Richter et al. (2005) who suggested that disruption of fluency of speech in children with MSD in the context of PFS may also be caused by lesions of the deep cerebellar nuclei more specifically the interposed nuclei and parts of dentate nuclei cannot be excluded on the basis of our findings. The hypothesis that MSD in the context of PFS is due to impairment of higher speech functions considers PFS as a particularly acute form of the Cerebellar Cognitive Affective Syndrome (CCAS).[68] CCAS was first described in adults with cerebellar lesions of mixed etiologies and consists of four major symptoms: disturbances of 1) executive function, 2) visual spatial performance, 3) linguistic processing and 4) affective regulation.[69] Executive impairments include deficits in working memory, motor or ideational set shifting, and perseverations. Verbal fluency may be reduced, even to the point of mutism.[70] Visual spatial impairment results in difficulties to copy figures or diagrams. Linguistic abnormalities may include anomia, agrammatic speech, abnormal syntactic structure, abnormal prosody, and also high pitched, hypophonic whining. Abnormal behavior may present as flattening of affect, alternating or coexistent disinhibited behavior manifesting, for example, as inappropriate or impulsive actions. Regressive childlike behaviors and obsessive–compulsive behaviors can also occur. In addition autonomic changes may occur in CCAS, manifesting as bradycardia and syncope, or tachycardia in the setting of acquired panic disorder.[20,70,71]

Neuroanatomical tracing studies show how the cerebellum is an integral node in the distributed neural circuits subserving cognition, emotion, and motor function.[68,71] Schmahmann (2001) conceptualized in the dysmetria of thought hypothesis that 1) a universal cerebellar transform facilitates automatic modulation of behavior around a homeostatic baseline, 2) the behavior that is being modulated is determined by the specificity of discretely organized

functional anatomic sub-circuits or loops, within the frame work of the cerebro-cerebellar system .The cerebro-cerebellar system is intricately organized and constructed to subserve the multitude of sensorimotor as well as higher order behavior patterns identified in the clinic.[68] Damage to the cerebellar component of the distributed neural circuit subserving sensorimotor, cognitive, and emotional processes disrupts the universal transform, and manifests as ataxia when the sensorimotor anterior part of the cerebellum is involved and as CCAS symptoms when the posterior part of the cerebellum including the vermis is involved in a lesion. In the children with PFS in our study, behavioral and speech symptoms belonging to CCAS were largely transient and present in varying combinations, supporting the hypothesis of impairment of higher functions after cerebellar lesions. However, in this study as well as in earlier studies in children with PFS after cerebellar surgery, not necessarily all symptoms from all four domains were observed in one subject. [20,21,72,73,74] We therefore conclude that in children CCAS may constitute a rather loose complex of symptoms with variable composition.[22] In a critical review, Frank et al. (2007)[75] question the role of the cerebellum in cognitive functions. They argue that many findings frequently cited to support cerebellar involvement in cognitive functions either depend on motor components of tasks or may at least in part be caused by independent factors. Because of the transient nature of PFS, they suggest a complex interaction of cerebellar lesion, brainstem affection and hydrocephalus, in combination with the incomplete development of speech motor control and language in childhood.[35]

SPECT scan findings

The SPECT scan findings in this study support the hypothesis that the surgical cerebellar trauma in children with PFS leads to functional impairment of the deep cerebellar nuclei bilaterally and that this has a widespread effect on supratentorial brain structures.[45] This supratentorial cerebral hypoperfusion is thought to be induced by usually transient perturbation of the dentato-thalamo-cortical pathways.[17] This phenomenon of diaschisis was initially described by Von Monakow (1914)[76] as focal cerebral lesions that cause temporary impairment of function at a remote site in children.[76] The exact pathophysiological mechanism of this phenomenon still remains unclear. The delayed onset and sub acute development of symptoms in the two children with arterial ischemic infarctions in supratentorial regions after cerebellar tumor surgery may represent the extremes of the spectrum i.e., relatively mild to moderate transient (see Fig 2C) hypoperfusion in MSD and PFS on the one hand and more severe hypoperfusion leading to cerebral ischemic supratentorial infarction on the other hand.[49] The hypothesis of diaschisis induced PFS explains the reversibility and variation in duration of symptoms, which far exceeds the duration of symptoms expected when caused by postoperative edema or ischemia of median cerebellar structures. In addition, this observation supports the concept that the cerebellar lesion per se is not the cause of the cognitive and emotional deficits, but rather that the role of the cerebellum is a moderator of

cognitive and emotional functions by means of its anatomic sub-circuits or loops within the cerebro-cerebellar system.[71]

In all children with PFS and mutism, severe hypoperfusion on SPECT scan was present at the tumor resection site bilaterally in the centre of the cerebellum, in the region of the deep cerebellar nuclei (see Fig 2A). In contrast, the children without PFS and the children with PFS who were not mute showed less severe or unilateral perfusion abnormalities of the central cerebellar region. In agreement with earlier SPECT scan findings in this group, cerebellar hypoperfusion on SPECT scan considerably diminished at follow-up, which may be a reflection of the transient nature of PFS.[42,46]

In a SPECT scan study in patients with and without mutism following posterior fossa surgery, Ersahin et al. (2002) did not find a significantly different pattern of reduction of cerebral blood flow in different supratentorial areas between groups.[46] They postulated that the hypoperfusion in the supratentorial areas was related to the ventricular dilatation at the moment of the SPECT scan because of the similarity of their SPECT scan findings to those in children with normal pressure and obstructive hydrocephalus. In our patients, we could not confirm a correlation with PFS and pre- or postoperative hydrocephalus. We could also not demonstrate a relationship between duration of all PFS symptoms and severity and location of hypoperfusion in supratentorial regions. Germano et al. (1998) reported that SPECT scans of their patients with postoperative mutism disclosed a marked reduction of cerebral perfusion in the right-fronto-parietal region in one patient and in the left fronto-temporo-parietal region in another patient.[42] Sagiuchi et al. (2001) showed reduced cerebral blood flow in the bilateral thalami, bilateral medial frontal lobes and left temporal lobe in addition to the cerebellar vermis and both cerebellar hemispheres in a seven-year-old boy after medulloblastoma surgery.[44] We found significant correlations between duration of mutism in the children with MSD and SPECT scan hypoperfusion in the left temporal lobe, the right frontal lobe, and the right and left basal nuclei. These findings support the hypothesis that speech dysfunction in PFS is associated with functional disruption of the cerebellar–cerebral pathways connecting the cerebellum to the frontal areas that are involved in planning and initiation of motor activities, including speech. Speech dysfunction has been described after lesions of either the left or right supplementary motor cortex, which is located on the mesial aspect of the frontal lobe anterior to the motor cortex.[78] Cortical hypoperfusion on SPECT scan in the left frontal medial area has also been reported after cerebellar infarction in the distribution area of the superior cerebellar artery, suggesting functional disruption of the pathways connecting the cerebellum with the contralateral frontal region through the phenomenon of crossed cerebellar–cerebral diaschisis.[79] In this adult patient neurobehavioral symptoms compatible with the CCAS syndrome were found as well as transient mild transcortical sensory aphasia and in addition visual dyslexia and surface dysgraphia.[79]

Hypoperfusion in the occipital regions did not exclusively occur in the children with transient cortical blindness. However, hypoperfusion in occipital cortical regions was more severe in these children in comparison to the children who did not have transient cortical blindness. We did not find hypoperfusion of the thalamic nuclei in all children but the observation of compulsive pre-sleep behavior in one child, a syndrome which until now was only described after bilateral lesions of the paramedian thalamic nuclei, points to the thalamus as an important relay centre for the phenomenon of diaschisis after cerebellar surgical trauma. In agreement with the positron emission tomography findings of a reduction in frontal lobe metabolism of Terao et al. (1993) in a patient with compulsive pre-sleep behavior,[62] the SPECT scan in our patient also showed bilateral frontal hypoperfusion.

The observation of extrapyramidal symptoms such as orofacial dyskinesias in five children as well as a bilateral diminished blood flow bilaterally in the basal ganglia suggests that in addition to the cerebello-thalamo-cortical route also the more indirect cerebello-thalamo-striatal cortical pathway is involved in transmitting the transneuronal phenomenon of diaschisis.[80] The basal ganglia and the cerebellum are not only involved in motor planning and control, but also in processing language and behavior. Booth et al. (2007) argued that they have differential functions, such that the putamen engages in cortical initiation while the cerebellum amplifies and refines the signal to facilitate correct decision-making.[81] Hypofunction of the basal ganglia that are functionally strongly connected with different parts of the frontal lobe by reciprocal cortical–striatal loops may explain some of the more frequent behavioral symptoms we observed in our patients, which were diminished facial expression in all children and severe apathy in 70%. It may also be responsible for the reduction of spontaneous behavior, which frequently occurred at long-term follow-up in children after resection of a cerebellar pilocytic astrocytoma.[22]

If the deficits we observed in the children with PFS can be interpreted as an effect of diaschisis, it has to be concluded that the reciprocal cerebro-cerebellar connections are operative at a very early age. The susceptibility of the pediatric age group to PFS after cerebellar damage is as yet unexplained, but may be due to relative immaturity of synapses or fiber tracts within the network. Our finding of a significant correlation between duration of mutism and severity of neurologic motor symptoms may reflect the severity and extent of the shutdown of neurotransmission within this cerebellar–cerebral pathway. The significant correlation of older age at time of PFS and longer duration of PFS we found in this study may be explained by the hypothesis that in young children more complex cognitive and behavioral skills are in part prefunctional at the time of the lesion and for this reason the full impact of hypoperfusion will not be fully apparent shortly after surgery.[82] In contrast, the sequelae will be especially apparent in older children when hypoperfusion occurs in brain areas such as the frontal lobe, at a time when maturation occurs which is critical for development of social, behavioral and executive functioning skills.

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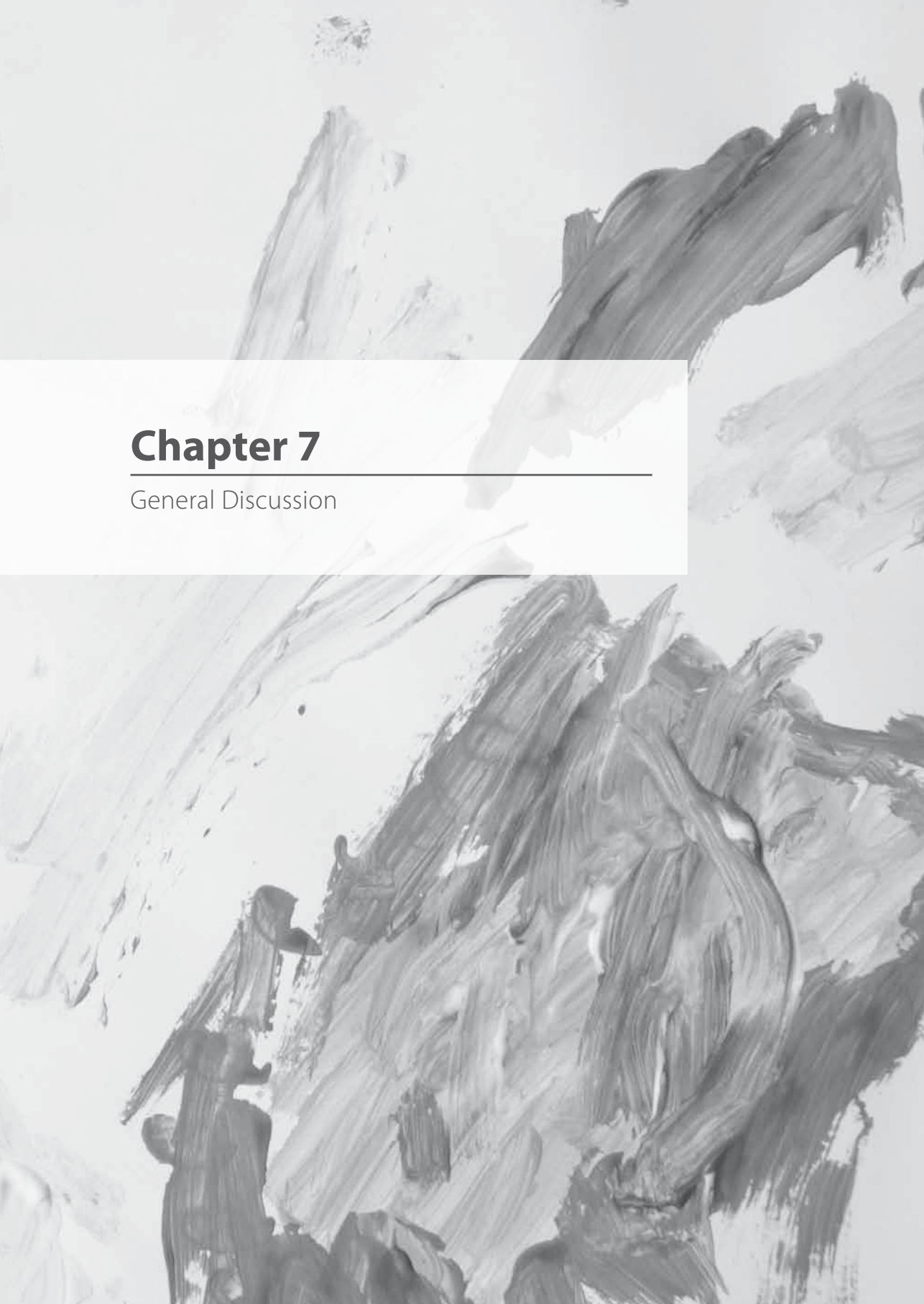

Chapter 7

General Discussion

Brain tumors are the most common solid tumors of childhood. The most frequently occurring histological tumor type is astrocytoma (40-50%).[1,2] The most common astrocytoma type in children is a low-grade astrocytoma (LGA).[2] This histologically benign tumor type may occur anywhere in the central nervous system. First choice treatment for LGA is total resection. Children with a diagnosis of LGA have a relatively high survival rate and their quality of life (QOL) is usually seen as "fares well".[3] They attend school and will participate in professional work. However, how they "fare" in real life at long-term is largely unknown. A wide variety of problems is described in small series only: neurologic impairments, cognitive deficits, behavioral and emotional dysfunction, and a lower QOL but a systematic assessment of all these aspects in larger series is lacking.[3-17]

Long-term neurologic impairments, cognitive deficits, behavioral and emotional dysfunctions are well known in children with another type of acquired brain injury (ABI) such as traumatic brain injury (TBI).[18-21] Late neurocognitive deficits in children with TBI could be problems with attention, speed, novelty learning, executive functioning, and language.[18] Twenty percent of children with severe TBI have a diagnosis of secondary attention deficit hyperactivity disorder (s-ADHD).[19] These children have more subtile memory or executive function problems than children with ADHD without TBI.[19] Problems with social-emotional functioning are emotional instability or diminished social problem solving skills in children after TBI[20] and behavioral impairments may include aggressive behavior, anger, impulsivity, anxiety, diminished self-control, diminished initiation, and inappropriate behavior.[21] These acquired neurocognitive, social-emotional, and behavioral problems in children with TBI necessitate attention to physical, cognitive and psychosocial outcome in children with ABI in general. We studied these outcome parameters in children treated for LGA.

Long-term outcome in children treated for LGA.

Neurologic outcome

We found neurologic impairments in 61% of the children treated for LGA. Motor and visual problems were most frequently revealed at neurologic examination and fatigue was most frequently mentioned as invalidating impairment. In a minority of patients, endocrine abnormalities, neglect, apraxia, aphasia, or dysarthria were found. Neurologic outcome depended on localization of the tumor. A supratentorial tumor more frequently resulted in visual disorders or visual field defects where as an infratentorial tumor more frequently caused motor problems such as ataxia, even almost eight years after diagnosis of LGA. Another study[4] on long term neurologic outcome in children treated for LGA revealed less motor and visual problems but the authors excluded exactly those tumors, the visual pathway and brain stem tumors, which resulted in more visual and motor deficits.

Fatigue is a well known invalidating impairment in adult cancer patients treated with radio- or chemotherapy.[22] Fatigue problems are more pronounced in adults with midline brain tumors in comparison with brain tumors situated in the hemisphere and in those with more severe neurologic impairments.[23] In one study fatigue was worse in adults with low-grade brain tumor than in a control group with hematologic malignancies suggesting that fatigue problems are not exclusevily due to chemotherapy.[24] Fatigue is commonly considered to have a multifactorial basis. Possible risk factors for fatigue after TBI are gender, depression, pain, sleep problems, motor, and memory dysfunction.[25] In another study in adults with TBI almost 60% of the fatigue score could be explained with poor sleep, lower vitamin D levels, and anxiety. These fatigue problems resulted in a lower educational level and a lower percentage of paid jobs in fatigued adults than in non-fatigued adults with TBI.[26] This suggests that fatigue is a major invalidating problem for participation in the adult society.

In children with ABI less is known about fatigue as risk factor for impairment of participation in society. Our group found invalidating fatigue problems in children with MS[27] or after pediatric stroke.[28] Four years after diagnosis 16% of children with MS had severe fatigue problems. This was related with depression and resulted in a lower QOL in the domains motor, cognitive functioning, and interaction with peers. Two years after diagnosis of pediatric stroke 12% of children mentioned fatigue problems. In children with brain tumors no research has so far been done. Regretfully, we did not systematically assess fatigue in all our studies, because at the start of our studies fatigue had not been recognized as a long-term residual complaint after LGA treatment. However, during the course of our studies we observed that fatigue was frequently mentioned by parents and patients themselves. For this reason, we decided to systematically include the variable fatigue in our last study in children with low-grade tectal tumor. A high percentage of these children suffered from fatigue, but the sample was small. Future research is necessary in children with LGA to study the effect of fatigue and related complaints on neuropsychologic deficits and to identify risk factors for fatigue in order to give an adequate neurorevalidation program.

Neuropsychologic outcome

All children treated for LGA had attention and speed problems. This implies that these specific cognitive deficits are independent of the site or treatment of the tumor and reflect a more global brain dysfunction.[29] ABI in children has often diffuse effects resulting in more basal cognitive function problems like attention, psychomotor, and learning deficits.[30,31] For example, children with focal hemispheric damage treated with hemispherectomy show a generalized pattern of cognitive deficits resulting in a general loss of intellectual impairment. [32]

In the group with supratentorial tumors we found specific neuropsychologic problems despite a normal intelligence: in the group of children with supratentorial hemispheric tumor

we found selective attention and executive functioning problems and only in the supratentorial left thalamic tumor group we found language and memory problems. This is in contrast to earlier described general intellectual deterioration and memory dysfunction.[4,10,11] In the study of Yule,[4] two children with cerebral hemisphere PA had a subnormal IQ of 87 one year after treatment. After treatment for temporal lobe astrocytomas five out of seven children were reported to have intellectual deterioration, learning disabilities or psychopathology.[10] The majority of 14 children with temporal lobe tumors had an increased risk for memory dysfunction, academic failure, and behavioral problems three years after treatment.[10] In our group only one child had a resection of the hippocampus, which is an important structure for memory functions. Sparing of global intelligence in comparison with these studies[4,10,11] may be explained by the fact that the children in our supratentorial group did not have radiotherapy, which can lead to intellectual deterioration or memory dysfunctions.[33] Also knowing that therapy resistant epilepsy may lead to intellectual decline,[34] seizures were well controlled in our patients with epilepsy.

In the total group with infratentorial tumors (the cerebellar and brain stem group) we found deficits in language, visual-spatial memory, executive, social and behavioral functioning. Children treated for a brainstem LGA had problems with speed, sustained attention, verbal and visual-spatial memory, verbal intelligence, and naming. Traditionally the brain stem is not regarded as a structure that mediates cognitive functions. A possible explanation could be disruption at pontine level of fibers modulating behavior and cognition in the reciprocal cerebello-ponto-cerebral circuitry.[35,36]

The only difference between children treated for a tectal and non-tectal tumor was a higher verbal intelligence in the non-tectal tumor group. A possible explanation for this difference is that the children in the non-tectal tumor group had a shorter period of raised IntraCranial Pressure (ICP) and we found a relation between lower verbal intelligence and a longer period of raised ICP. This implies that a long period of hydrocephalus negatively influences verbal intelligence. Further analysis in the tectal tumor group revealed that almost all cognitive problems were found in the group of children with a severe hydrocephalus and a long history of symptoms of raised ICP. This implies that not the location of the tumor, but rather the severity of the hydrocephalus plays a causative role in cognitive impairments. However, optimal treatment of hydrocephalus did not prevent persisting memory and attention problems in the group of children with normal ventricle size. This suggests that these remaining symptoms were a result of long lasting negative effects of raised ICP on volume and function of fiber tracts reciprocally connecting cerebellum and cortex.

In the cerebellar group we recorded long-term apraxia, motor neglect, dysarthric features, as well as language, sustained attention, visual-spatial, executive, memory, and behavioral

problems. These impairments were observed in various combinations and to different degrees. According to the literature there are crossed cerebro-cerebellar connections, which are important in modulation of executive processes, temporal ordening and timing, attentional mechanisms, visual-spatial processing, memory and learning.[37] Our findings do not unequivocally support the concept of cerebellar lateralization of cognitive functions. Only three out of 14 children with an incision site in the right or left cerebellar hemisphere showed a pattern of impairments compatible with a crossed cerebro-cerebellar organization of cognitive functions. A possible explanation is that in case of a very large cerebellar hemisphere astrocytoma the neurosurgical procedure causes diaschisis extending to both cerebral hemispheres. SPECT scan findings in one child with both right parieto-occipital and left occipital hypoperfusion after left cerebellar hemispheric astrocytoma surgery support this assumption.[38] Another possibility could be that the hydrocephalus and the raised ICP results in hypoperfusion of the area of the arteria basilaris, but we do not have pre-operative SPECT scan findings to check this. Also in children, lateralization of cerebro-cerebellar pathways may not as yet be completed due to relative immaturity of synapses or fiber tracts within the network. [39] Also crossed cerebellar diaschisis of glucose metabolism is not as prominent in children as in adults

Psychosocial outcome: education, behavior, and QOL

Our educational data show that almost half of the children after LGA treatment needed special education services. Risk factors are relapse or a younger age at diagnosis. This percentage far exceeded the national average of 5% in the Netherlands. In British children with severe TBI 29% used educational needs[20] and another study showed that cognitive services were the most frequent type of service associated with unmet or unrecognized health care needs. [19] Children treated for LGA who need special assistance have a lower QOL than children who do not need such assistance. This illustrates that cognitive deficits occurring in such children after treatment of LGA not only have implications for their school career but also for their perception of QOL.

The social consequences of impairments and disabilities, i.e. the handicaps, were evident in the domains of relationships and behavior. Children in this study mix with friends less and develop fewer activities outside school. The kind of social problems are in accordance with those displayed by survivors of childhood cancer in general and do not seem to be specific for survivors of brain tumors, but they differ in severity of the social problems.[41] The behavioral problems are most pronounced in the group of children treated for an infratentorial tumor and this is comparable with the pre-surgical behavioral problems in children treated for posterior fossa tumors.[42] This implies that also the tumor and not only the surgical lesion seems to play an important role in the origin of behavioral problems.

Children, parents, and teachers rate the severity of behavioral problems differently. The different ratings in our study may also be explained by what is often being referred to as 'resilience' and can also be described as coping or adaptation to impairments. This is supported by the fact that survivors of childhood cancer tend to judge their own ability to cope as superior.[41]

Parents report a decreased QOL in all scales except for positive and negative emotions. Children indicate a low QOL in motor, cognitive, and social functioning. The lower QOL in our study is similar to that displayed in another study on survivors of a cerebellar pilocytic astrocytoma.[3] Risk factors for a lower QOL are relapse and age.

Risk factors for cognitive dysfunctions

Age

Our studies demonstrate that there are three inter-related age effects: age at diagnosis, interval between diagnosis and assessment, and age at assessment.[43] Children who were diagnosed during adolescence report a lower QOL in social functioning than children who were diagnosed at a younger age. This reflects the overall importance of establishing socializing and intimate relationships during adolescence.

A younger age at diagnosis as risk factor for more severe impairment of cognitive functions and academic achievement is also described in studies on survivors of childhood cancer[44] and in children with traumatic brain injury.[43,45] This phenomenon could be explained by the vulnerability theory: children with a diagnosis and treatment at a younger age have to learn new skills with already defective basal functions.[44] For the other age effects (interval and age at assessment) there could be a biologic[46] or a behavioral explanation.[43] In irradiated children the late effects of radiotherapy interfering with neuronal development lead to cognitive decline.[46] As expected we found an interaction effect between age and radiotherapy on attention. However, also in children without radiotherapy cognitive problems become apparent years after diagnosis of LGA. We found significant correlations between age at the time of assessment and behavior, QOL or cognitive functioning. These correlations illustrate that behavioral, physical, motor, cognitive, and social problems become more manifest over the years. A more developed sense of self-reflection cannot be held responsible for these relations, as parents also signal more problems when their children reach adolescence. It seems that some of these problems gradually become apparent years after the diagnosis and the treatment. It has been suggested that "early brain damage may have a cumulative effect on ongoing development, with increasing deficits emerging through childhood as more functions are expected to mature and need to be subsumed within the undamaged tissues".[47, p 107] These new long-term problems could result from changes during the further

postnatal development leading to disruption in pathways that fail to develop properly as a result of the tumor or surgical lesion.[17] This phenomenon of "growing into deficits" has played a role in the development of long-term deficits.

Hydrocephalus

We did find that severity of ventricle dilatation and a longer period of raised ICP negatively influenced attention, language comprehension, executive functioning deficits, and behavior in children with infratentorial tumors in chapters 4 and 5. Treatment of ventricle dilatation with a Ventriculo-Peritoneal (VP) -drain results in better functioning in the whole group of children with LGA in chapter 2. This is in agreement with the finding in adult patients with aqueduct stenosis that cognitive recovery correlates well with the reduction of ventricular size.[48] Despite maximal neurosurgical treatment, hydrocephalus persisted, especially in children with a long history of symptoms of raised ICP.

Cognitive deficits are well studied in children treated for congenital hydrocephalus. In children with spina bifida that were treated for congenital hydrocephalus, intelligence is in the average, low-average, and borderline range.[49] They have problems with arithmetic, visual and tactile perception, motor speed, and visual-motor integration. [49] Children with a congenital aqueduct stenosis have a lower non-verbal intelligence, borderline mean IQ, and motor problems. [50-52] It has been suggested that in these children the cluster of cognitive deficits is comparable with that of the Non-verbal Learning Disabilities (NLD) syndrome. [53] NLD is characterized by impairments in three cognitive domains: visual/spatial/organizational, sensorimotor, and social.[53] The white matter model attempts to explain the syndrome of NLD. [53] The hypothesis is that NLD will manifest to the extent that white matter in the whole brain is underdeveloped, damaged or dysfunctional because of hydrocephalus, TBI or acute lymphocytic leukemia or other causes that damage white matter.[53] The persistence of wider ventricles cq perturbations of white matter without signs of raised ICP is a predictor of poor neuropsychologic functioning. We postulate that this is due to the relative loss of cerebral white matter and failure to develop white matter at a rate appropriate to the developmental stage of the child due to longstanding raised ICP.

It is important to decrease ventricular size as much and as soon as possible also in children who do not have clinical symptoms or signs of raised ICP in order to obtain an optimal condition for a good cognitive development. Optimal and timely treatment of hydrocephalus did not prevent persisting memory and attention problems in the group of children with normal ventricle size and these problems are comparable with cognitive deficits in children treated for congenital hydrocephalus without tumor treatment. [49-52] This implies that the remaining symptoms were a result of long lasting effects of raised ICP. This is supported by findings in a study in which children with mutism and subsequent dysarthria (MSD) after cerebellar

tumor surgery had postoperative significantly more persisting hydrocephalus than children without MSD after surgery.[54] They concluded that hydrocephalus can be considered as a concomitant, but not a specific causing factor for behavioral and cognitive deficits like MSD.[54]

Postoperative Condition

Poor acute postoperative condition seems to be of prognostic importance for long-term neuropsychologic deficits, as relationships were found between the occurrence of MSD or severe postoperative ataxia and disorders of attention at long-term follow-up in chapter 5. Chemotherapy as treatment for LGA resulted in better executive functioning in chapter 2. The differential effect of radio- versus chemotherapy on cognitive functioning is well known and is explained by the loss of cerebral white matter and failure to develop white matter at a rate appropriate to the developmental stage of the child.[55] The more favorable effect of chemotherapy versus surgery can be explained by the fact that in children treated with chemotherapy, surgery was restricted to a diagnostic biopsy or a relatively small resection. This neurosurgical procedure limits the traumatic damage in comparison to a more extensive resection.

Posterior Fossa Syndrome (PFS)

The cluster of disturbances of executive function, impaired visual-spatial cognition, linguistic/speech difficulties, and personality changes may fit in the spectrum of cerebellar disorders of spontaneous speech and behavior such as MSD,[56] the posterior fossa syndrome (PFS),[57] or cerebellar cognitive affective syndrome (CCAS).[9] The concept of CCAS has been introduced in a study of adult patients with cerebellar lesions of mixed etiologies.[58] However, none of them presented all four core-features of the syndrome at the same time. In another study in adults with a unilateral cerebellar stroke matched with controls for age, gender and educational levels, patients did also not fulfill all criteria of CCAS.[59] The present study and earlier studies[8,9,60,61] recorded in children with cerebellar damage due to surgery, chemo- or radiotherapy, showed varying combinations of symptoms and signs belonging to CCAS, but failed to identify all four symptoms in one subject. As a syndrome is defined as a set of symptoms that occur together with sufficient frequency,[62] we conclude that although long-term cognitive disturbances definitely occur in children after cerebellar LGA treatment, "CCAS" in most children constitutes a rather loose complex of symptoms of variable composition within the different domains.

Different hypotheses to explain the origin of these syndromes are the paravermal surgical approach,[63] lesions of the deep cerebellar nuclei,[64] the anarthria hypothesis,[64] the impairment of higher order functions.[64] A paravermal surgical approach was introduced in order to prevent vermal damage in children with cerebellar tumors.[63] However, PFS continued to occur despite this change in practice that avoided the splitting of the vermis.[65] Consequently, vermal loca-

tion and surgical damage to the vermis cannot be the key determinants in the development of CCAS. The anarthria hypothesis considers MSD as the most severe form of dysarthria.[64] On the basis of studies in adults with cerebellar stroke and supported by functional MRI (fMRI) findings, the cerebellar regions crucial for the development of cerebellar ataxic speech are thought to be situated in the paravermal regions on either side in the superior cerebellum, corresponding with paravermal lobules VI and VII. [64,66,67] In our patients, surgical lesions were limited to the cerebellar midline and only occasionally extended into the left or right paravermal region. For these reasons, our findings do not support the anarthria hypothesis.

It is suggested that, although further data in the human literature are lacking, disruption of fluency of speech in children with MSD in the context of PFS may be caused by lesions of the deep cerebellar nuclei, more specifically the interposed nuclei and parts of dentate nuclei.[64] On the basis of our findings this hypothesis cannot be excluded.

The hypothesis that MSD in the context of PFS is due to impairment of higher speech functions considers PFS as a particularly acute form of CCAS.[68] Neuroanatomical tracing studies show how the cerebellum is an integral node in the distributed neural circuits subserving cognition, emotion, and motor function.[68,69] Damage to the cerebellar component of the distributed neural circuit disrupts the equilibrium and manifests as ataxia when the sensorimotor anterior part of the cerebellum is involved and as CCAS symptoms when the posterior part of the cerebellum including the vermis is involved in a lesion.[68] The SPECT scan findings in chapter 6 support the hypothesis that the surgical cerebellar trauma in children with PFS leads to functional impairment of the deep cerebellar nuclei bilaterally and that this has a widespread effect on supratentorial brain structures. This supratentorial cerebral hypoperfusion is thought to be induced by usually transient perturbation of the dentato-thalamo-cortical pathways.[70] This phenomenon of diaschisis was initially described as focal cerebral lesions that cause temporary impairment of function at a remote site in children.[71,72] The hypothesis of diaschisis-induced PFS explains the reversibility and variation in duration of symptoms, which far exceeds the duration of symptoms expected when it would be caused by postoperative edema or transient ischemia of median cerebellar structures. In addition, this observation supports the concept that the cerebellar lesion per se is not the cause of the cognitive and emotional deficits, but rather emphasizes on the role of the cerebellum as a moderator of cognitive and emotional functions by means of its anatomic sub-circuits or loops within the cerebro-cerebellar system.[69] The observation of extrapyramidal symptoms such as orofacial dyskinesias in five children in the study described in chapter 6 as well as a bilateral diminished blood flow bilaterally in the basal ganglia suggests that in addition to the cerebello-thalamo-cortical route, the more indirect cerebello-thalamo-striatal cortical pathway is involved in transmitting the transneuronal phenomenon of diaschisis as well.[73]

The behavioral problems as part of CCAS in children treated for a cerebellar LGA are very similar to those of our group of children treated for a tectal tumor with a severe hydrocephalus at time of assessment. Our results in the tectal group imply that part of the CCAS symptoms in children with a cerebellar tumor resection is not exclusively due to the cerebellar lesion or the resection or the tumor. Our findings strongly support the important concomitant role of raised ICP due to obstructive hydrocephalus. This dual hit causes cerebral dysfunction by direct compression of supratentorial fiber pathways of the cerebello-cortical circuitry. This hypothesis is in agreement with findings in a SPECT scan study in patients with and without mutism following posterior fossa surgery.[74] It was postulated that the hypoperfusion in the supratentorial areas was related to the ventricular dilatation at the moment of the SPECT scan because of the similarity of their SPECT scan findings to those in children with normal pressure and obstructive hydrocephalus.[74]

Compression of periventricular cerebral structures due to hydrocephalus in the developing brain has a negative effect, because more complex cognitive and behavioral skills are in part prefunctional at the time of the hydrocephalus and for this reason the full impact of hypoperfusion will not be fully apparent shortly after hydrocephalus.[43] Our dual hit model implies a complex interaction of cerebellar lesion and hydrocephalus and explains why PFS almost exclusively occurs in children.

The main conclusion of this thesis is that children with a LGA do not fare well, because they have long-term neurologic impairments, academic disabilities, handicaps in the domains of relationships and behavior, neuropsychologic deficits, and a lowered QOL. The deficits are caused by a complex interaction of different risk factors such as age at debut of the tumor, age at time of assessment, site of tumor, type of treatment, hydrocephalus, diaschisis, postoperative condition, and relative immaturity of synapses or fiber tracts.

Clinical implications

This thesis provides an overview of the long-term consequences for children with LGA and risk factors for adverse neurologic, cognitive, and behavioral outcome. For medical doctors it is important to recognize the late neuropsychologic effects of treatment of LGA in children, due to the growing into deficit phenomenon and to realize the adverse effect of hydrocephalus in combination with several other factors to cognitive development.

Now the neuropsychologic deficits in children after LGA treatment are identified, the next step is to investigate which type of rehabilitation or medication is most effective for these children. Up to now few studies have approached this problem. No definite conclusions can as yet be drawn, because of the small number of patients, the absence of pediatric patients, other causes of ABI, or short follow-up period. Also there are questions about the ecological validity of these interventions.

For example the computerized COGMED[QM] training[75] or the Amsterdamse Training voor Aandacht en Geheugen voor Kinderen (ATAG-K) training[76] may improve memory and attention dysfunctions, but the COGMED training has been evaluated in 18 adult patients with moderate or severe TBI and with a follow-up period of six months after training. The ATAG-K training has been done in 38 children with ABI but long-term follow-up is lacking. Also attention can improve with methylphenidate and modafinil seems to have a beneficial effect on processing speed in adult patients with cancer.[77] In pediatric cancer survivors at least one year after stop of treatment, attention improved after 1 month on methylphenidate.[78]

The Quality of Life In Motion (QLIM) study[79] is an ongoing study in which combined physical exercise and psychosocial training program has to improve physical fitness in children with cancer, but first the impact of fatigue on neuropsychologic functioning has to been investigated. Also the cognitive behavioral treatment protocol "Friends"[80] is an ongoing study in children with a brain tumor to diminish anxiety problems. Originally the program was designed for school children to cope with feelings of fear, worry, and depression by building resilience and self-esteem and teaching cognitive and emotional skills in a simple, well-structured format.

The studies described in this thesis illustrated that systematic neuropsychologic and behavioral follow-up in children with a relatively benign brain tumor as LGA with a good oncological prognosis is necessary to detect disturbances in these fields and to organize tailored interventions. Extending this concept to all children with a brain tumor, these studies resulted in the design of a Dutch national neuropsychologic follow-up protocol for children with a brain tumor and the start of the neuropsychologic taskforce within the Dutch Children's Oncology Group (DCOG).

Table 1 Summary of neuropsychologic outcome according to groups of tumor site

	Infratentorial			Supratentorial		
	Cerebellum	Tectum	Non-tectal brain stem	Hemisphere	Ventral midline	Dorsal midline
Attention	+	+	+	+	+	+
Speed	+	+	+	+	+	+
Language	+	+	+			+
Memory	+	+	+			+
Executive skills	+			+		
Visual-spatial skills	+					
Total intelligence						

Note + significantly different in comparison with Dutch norms

Due to this follow-up, cognitive and behavioral consequences of the disease are detected in time and result in adequate counseling for cognitive rehabilitation. The protocol partly prevents school problems, because it enables timely intervention. Although better information is at present given to parents about long-term deficits, a recent study showed that the after-care trajectory is still insufficient at this moment in the Netherlands.[81] Despite the fact that almost everyone received after-care, the delay to start with an intervention is too long and there is much self-referral. Greater alertness, a better organization and more manpower are necessary to improve the after-care trajectory.

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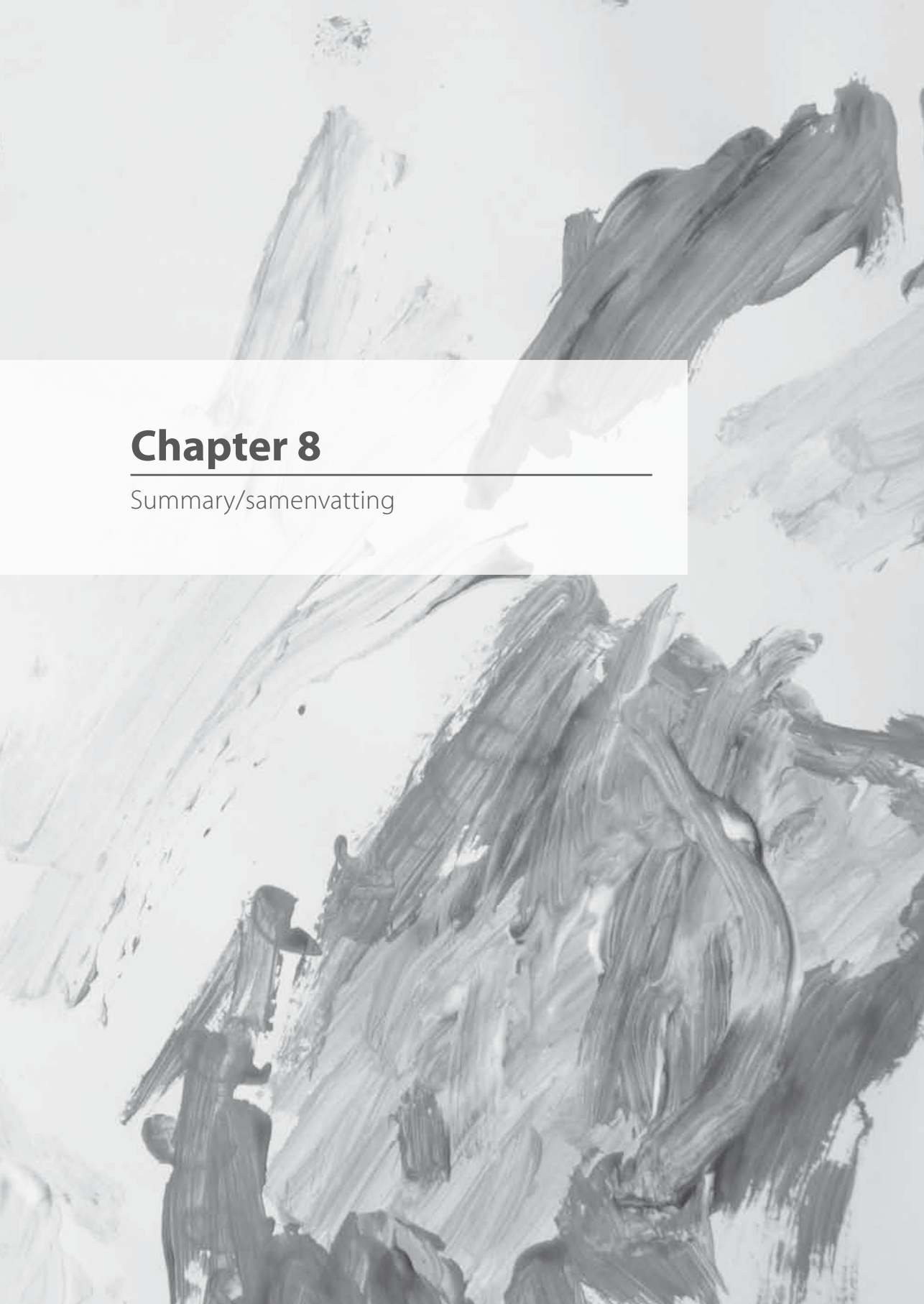

Chapter 8

Summary/samenvatting

SUMMARY

In **Chapter 1,** the literature is summarized about functional outcome, neurologic, cognitive, and behavioral consequences in children treated for low-grade astrocytoma (LGA). Outline and purpose of the study is described.

In **Chapter 2** we describe a prospective long-term follow-up study of 67 children treated for LGA grade 1, pilocytic astrocytoma (PA), between 1993-2004. After 3 years, all children with PA have problems with sustained attention and speed. In the infratentorial group there are deficits in verbal intelligence, visual-spatial memory, executive functioning, and naming. Quite surprisingly verbal intelligence and verbal memory problems occur in the brain stem tumor group. The supratentorial hemispheric tumor group has additional problems with selective attention and executive functioning. The supratentorial midline tumor group displays no extra impairments, but more specifically the dorsal supratentorial midline tumor group had problems with language and verbal memory. Predictors for a lower cognitive functioning are hydrocephalus, radiotherapy, residual tumor size or age. Predictors for a better functioning are treatment of hydrocephalus with Ventriculo-Peritoneal (VP) shunt or chemotherapy. Almost 60% of children had problems with academic achievement and risk factors were relapse and younger age at diagnosis. Despite a normal intelligence, children treated for a PA have long-term invalidating cognitive impairments. Adequate treatment of hydrocephalus is important for a better cognitive outcome. Even children without initial severe deficits may develop cognitive impairments years after diagnosis, partly because of the phenomenon "growing into deficit" with devastating implications for their academic achievement and Quality Of Life (QOL).

In **Chapter 3** we describe functional outcome in the following domains: impairments, disabilities, handicaps, and QOL in a consecutive series of 38 children. Follow-up ranged from 3 years and 7 months to 11 years and 4 months after diagnosis. Sixty–one percent of children had impairments and 10% a severe disability. Handicaps were found in the domains of relationships, school, and behavior. Children treated for supratentorial tumors needed significantly more special education and children treated for an infratentorial tumor had significantly more behavioral and social problems. QOL was significantly decreased in all domains except for emotions. Children with a diagnosis in adolescence reported a lower QOL in social functioning than younger children. At long-term follow-up children with LGA have a poor functional outcome depending on tumor site, age of diagnosis or age at time of assessment, and relapse. Children without neuropsychologic deficits may develop severe cognitive, social, and behavioral deficits years after diagnosis because of the phenomenon of "growing into deficit". Therefore we advise a long-term follow-up of children who are treated for LGA at a young age, to detect and subsequently offer support focused on the medical and cognitive impairments as well as on the behavioral and social consequences of their disease.

In **Chapter 4** we focus on a consecutive series of 12 children with low-grade tectal tumor diagnosed in our hospital between 1994-2008. Neurologic, neuropsychologic, and radiologic data were prospectively collected. Follow-up ranged from 1 year to 10 years. At follow-up, the most frequent neurologic disability was fatigue. In addition they scored lower on sustained attention, long-term memory and they also suffered from behavioral problems. Factors influencing cognition were duration of symptoms of raised intracranial pressure (ICP) and persisting severe hydrocephalus. In 60% of children the cognitive problems were so severe that they needed assistance of special services at school. At long-term, children with a low-grade tectal tumor display invalidating neuropsychologic impairments resulting in educational problems. Adequate and timely treatment of hydrocephalus may result in better cognitive functioning. Our findings suggest that part of the symptoms of the cerebellar cognitive affective syndrome (CCAS) may not have exclusively resulted from a cerebellar lesion itself but also from a cerebral dysfunction or compression of supratentorial structures in the cerebello-cortical circuitry due to the obstructive hydrocephalus.

Chapter 5 describes a consecutive series of 23 children treated for cerebellar PA. Long-term apraxia, motor neglect, dysarthric features, as well as language, sustained attention, visual-spatial, executive, memory, and behavioral problems were observed in various combinations and to different degrees. No clear pattern of neurocognitive disturbances could be discerned in this group. In addition significant relationships were revealed between severity of preoperative hydrocephalus and disturbances of visual-spatial skills. The high percentage of children who needed special education reflects the severity of the impairments.

Chapter 6 focuses on all children with a cerebellar tumor treated in ErasmusMC/Sophia between 1989-2007 in order to identify the Posterior Fossa Syndrome (PFS). PFS occurred in 41 of 148 children. During recovery, all children with PFS were dysarthric, but only in a few speech features specific for cerebellar dysarthria occurred. A significant correlation was found between duration of mutism and severity of neurologic symptoms in the acute phase. Significant correlations were also found between duration of mutism and abnormalities on SPECT scans of the left temporal lobe, the left and right basal nuclei, and the right frontal lobe. In this study, impairments of higher cognitive functions were observed in the context of PFS. They varied in severity and composition between children with symptoms fitting into the spectrum of the CCAS. SPECT scan findings suggest that these impairments are secondary to supratentorial metabolic hypofunction following cerebellar surgery.

NEDERLANDSE SAMENVATTING

In **Hoofdstuk 1 -**de introductie- wordt een overzicht gegeven van alle studies die over functionele uitkomst en over neurologische, cognitieve en gedragsmatige gevolgen gaan van kinderen, die behandeld zijn voor een laaggradig astrocytoom.

Hoofdstuk 2 beschrijft een prospectieve studie van 67 kinderen, die behandeld zijn voor een pilocytair astrocytoom (PA) in 1993-2004. Alle kinderen met een PA hebben problemen met de volgehouden aandacht en met het tempo. In de groep kinderen met een infratentoriële PA zijn er ook tekorten in verbale intelligentie, visueel-ruimtelijk geheugen, executief functioneren en het benoemen. De problemen met de verbale intelligentie en het verbale geheugen komen vooral voor bij kinderen met een PA in de hersenstam. De kinderen met een supratentoriële hemisfeer tumor hebben naast de tempo- en volgehouden aandachtsproblemen ook bijkomende problemen met de selectieve aandacht en het executief functioneren. De kinderen met supratentoriële midline tumoren hebben geen extra stoornissen, echter wanneer er specifiek gekeken wordt naar de groep met dorsaal gelegen supratentoriële midline tumoren, dan blijkt dat er ook problemen zijn met taal en verbaal geheugen. Voorspellers voor een slechter cognitief functioneren zijn hydrocephalus, radiotherapie, tumorrest of leeftijd. Voor een beter cognitief functioneren zijn dit chemotherapie en de behandeling van de hydrocephalus. Bij 60% van de kinderen worden er problemen op school geconstateerd. Risicofactoren hiervan zijn een recidief of een jonge leeftijd ten tijde van de diagnose. Ondanks een normale intelligentie hebben kinderen, die behandeld zijn voor een PA, op lange termijn invaliderende cognitieve stoornissen. Adequate behandeling van de hydrocephalus is belangrijk voor een betere cognitieve uitkomst. Zelfs wanneer kinderen eerst geen cognitieve stoornissen hebben, kunnen er jaren na diagnose toch cognitieve stoornissen ontstaan, gedeeltelijk vanwege het "growing into deficit" fenomeen. Dit heeft desastreuze gevolgen voor schoolprestaties en kwaliteit van leven (KvL).

In **Hoofdstuk 3** rapporteren wij ernstige beperkingen en stoornissen in een opeenvolgende serie van 38 kinderen, die behandeld zijn voor een laaggradig astrocytoom (LGA). Er zijn handicaps in het domein van relaties, school en gedrag. Kinderen behandeld voor een supratentoriële tumor hebben significant meer speciaal onderwijs nodig en kinderen, die behandeld worden voor een infratentoriële tumor hebben significant meer gedrags- en sociale problemen. De KvL is op alle domeinen laag met uitzondering van emoties. Kinderen met een diagnose in de pubertijd geven een verlaagde KvL aan op sociaal gebied. Op de lange termijn hebben kinderen met een LGA een slechte functionele uitkomst en dit hangt af van de plaats van de tumor, leeftijd en of er sprake is van een recidief. Kinderen zonder stoornissen kunnen jaren na diagnose ernstige cognitieve, sociale en gedragsmatige problemen ontwikkelen vanwege het "growing into deficit" fenomeen. Wij adviseren daarom een

lange-termijn follow-up voor kinderen, die behandeld zijn voor een LGA op jonge leeftijd om zo vroeg mogelijk medische en cognitieve stoornissen als wel de gedragsmatige en sociale consequenties van hun ziekte vast te stellen en aansluitend begeleiding te bieden.

In **Hoofdstuk 4** beschrijven we een opeenvolgende serie van 12 kinderen met een laaggradige tectum tumor. Kinderen met deze tumor scoren significant lager op volgehouden aandacht en het lange termijn geheugen. Deze uitkomst wordt beïnvloed door leeftijd, het interval tussen diagnose en testafname, hydrocephalus en de duur van de verhoogde intracraniële druk. Ouders observeren significant meer gedragsproblemen. Kinderen geven zelf aan dat ze alleen minder doen in hun vrije tijd. Er worden ernstige cognitieve en gedragsmatige problemen gezien bij kinderen met een ernstige hydrocephalus ten tijde van de testafname zonder symptomen van een verhoogde intracraniële druk. De neuropsychologische problemen hebben als gevolg, dat er meer kinderen in het speciaal onderwijs en meer kinderen op school met een leerling-gebonden financiering zitten.

Hoofdstuk 5 beschrijft een opeenvolgende serie van 23 kinderen, die behandeld worden voor een cerebellaire PA. Lange-termijn gevolgen komen tot uiting in een apraxie, een motor neglect en dysarthrische kenmerken in de spraak. Ook worden er problemen gezien met de taal, de volgehouden aandacht, de visueel-ruimtelijke functies, de uitvoerende controle functies, het geheugen en het gedrag. De kinderen laten verschillende soorten problemen in verschillende mate van ernst zien. Er wordt geen duidelijk patroon van neurocognitieve stoornissen gezien. Verder wordt er een significante relatie berekend tussen de ernst van de pre-operatieve hydrocephalus en visueel-ruimtelijke vaardigheden. Het hoge percentage kinderen, die naar het speciaal onderwijs gaan reflecteert de ernst van de neuropsychologische beperkingen.

Hoofdstuk 6 beschrijft alle kinderen met een cerebellaire tumor om het posterieur fossa syndroom (PFS) te kunnen onderzoeken. PFS komt voor in 41 van de 148 kinderen. Tijdens het herstel zijn alle PFS kinderen dysarthrisch, maar een paar hebben spraakkenmerken specifiek voor een cerebellaire dysarthrie. Een significante relatie wordt gevonden tussen de duur van het mutisme en de ernst van de neurologische symptomen. Ook worden er significante relaties berekend tussen de duur van het mutisme en de afwijkingen op de SPECT scan bij de temporaal kwab, de linker en rechter basale kernen en de rechter frontaal kwab. In deze studie worden er ook hogere cognitieve functiestoornissen geobserveerd in de context van PFS. Deze variëren in ernst en samenstelling tussen de kinderen en passen in het spectrum van het cerebellair cognitief affectief syndroom (CCAS). SPECT scan bevindingen suggereren ook dat deze beperkingen het gevolg kunnen zijn van metabolische hypofunctie na een cerebellaire operatie.

DANKWOORD

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Beste Coriene, jij bent een echte mensendokter, maar je kan ook zeer goed je collega's motiveren. Nadat ik mijn eerste artikel onder in de kast had gegooid, omdat ik gescoopt was in mijn naïviteit, wist jij het op een zeer positieve en uiteindelijk zeer geslaagde manier weer uit de kast te krijgen. Naast dat je goed jouw enthousiasme en kritisch kijk op mij hebt overgebracht, heb jij mij een hele range aan dingen bijgebracht. Deze zijn zeer uiteenlopend van poezen, wijze levenslessen, het grootbrengen van kinderen tot aan nieuwe boeiende ideeën voor komende onderzoeken.

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CURRICULUM VITAE

De auteur werd geboren op 04-09-1975 te Amsterdam. Zij begon haar opleiding op de HAVO voor Muziek en Dans in Rotterdam en stapte in het derde jaar over naar de OSG De Glopper te Capelle aan den IJssel. In 1993 slaagde zij voor haar bèta eindexamen op de Glopper. In 1993 begon zij na uitgeloot te zijn voor de studie geneeskunde de studie Psychologie op de Vrije Universiteit. In 1997 behaalde zij haar doctoraal als kinder- en jeugdpsycholoog aangevuld met medische en neuropsychologische vakken. In 1998 behaalde zij de diagnostiek aantekening NIP en in 1999 behaalde zij de NIP registratie als kinder-en jeugdpsycholoog NIP. In 2000 werd zij toegelaten tot de overgangsregeling Gezondheidszorg psycholoog, waar zij in 2003 haar BIG registratie als GZ-psycholoog behaalde. In 2010 behaalde zij eveneens via de overgangsregeling de BIG registratie voor Klinisch Neuropsycholoog. In 1997 liep zij stage in het Paedologisch Instituut te Duivendrecht op de afdeling Neuropsychologie en Leerproblemen. Ook rondde zij haar scriptie over dyslexie af binnen het Paedologisch Instituut bij Prof D. Bakker. In 1997 werkte zij na haar stage als vrijwilligster binnen het Paedologisch Instituut te Duivendrecht binnen de groep Neuropsychologie. In 1998 heeft zij gewerkt op de afdeling Kinder- en Jeugdpsychiatrie van het ErasmusMC/Sophia als werkervaringsplaats. Zij werkt sinds 1998 op de afdeling Kinderneurologie en sinds 2003 ook op de afdeling Kinderoncologie van het ErasmusMC/Sophia. Vanaf 1998 is zij begonnen met het volgen van kinderen met hersentumoren en momenteel worden alle kinderen systematisch gevolgd binnen het Sophia Kinderziekenhuis. Vanuit deze patiëntenzorg ontstond de interesse in het wetenschappelijk onderzoek en is er in de loop van de jaren veel data verzameld en dit is vertaald in een betere patiëntenzorg. In 2000 heeft zij gewerkt op de afdeling Neuropsychologie van het AZU/Wilhelmina kinderziekenhuis. Sinds 2008 werkt zij als docent Neuropsychologie voor kinderen voor de Centrale RINO in het curriculum voor de opleiding tot GZ-psycholoog. Verder is zij verbonden als docent aan de minor Kinderoncologie. Zij heeft als (principal) investigator meegewerkt aan verschillende internationale en nationale wetenschappelijke studies. Momenteel is zij voorzitter van de werkgroep Neuropsychologie binnen het SKION en werkt zij mee aan het Programma van Eisen (PvE) voor het nieuwe Nederlands Kinderoncologisch centrum (NKOC). In 2003 trouwde zij met Rutger Fieseler, in 2006 werd haar zoon Silvijn geboren, in 2008 kwam dochter Marie-Lise en in 2011 zoon Sweder.

LIST OF PUBLICATIONS

This thesis

1. Aarsen FK, Van Dongen HR, Paquier PF, Van Mourik M, Catsman-Berrevoets CE. Long-term sequelae in children after cerebellar astrocytoma surgery. *Neurology* 2004;62:1311-1316.
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Other publications

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13. Arts WF, Aarsen FK, Scheltens-de Boer M, Catsman-Berrevoets CE. Landau-Kleffner syndrome and CSWS syndrome: Treatment with intravenous immunoglobulins. *Epilepsia* 2009;50:55-58.
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20. De Smet HJ, Catsman-Berrevoets C, Aarsen F, Verhoeven J, Mariën P, Paquier PF. Auditory-perceptual speech analysis in children with cerebellar tumors: A long-term follow-up study. *Eur J Paediatr Neurol* 2012;16:141-149

ERASMUS UNIVERSITEIT ROTTERDAM

PhD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student: Femke K. Aarsen
PhD period: 2002-2012
ErasmusMC Department: Pediatric Neurology
Promotor: Prof. Dr. W.F.M. Arts
Co-promotor: Mevr. Dr. C.E. Catsman-Berrevoets

1. PhD training	Year	Workload (ECTS)
General courses		
Diagnostiek bij een vermoeden van seksueel misbruik bij kinderen	2000	1.0
Rationeel Emotieve Therapie en cognitieve therapie	2001	1.5
Lichamelijke klachten bij kinderen	2001	1.4
Kindertekeningen	2001	0.4
Psychodiagnostiek bij adolescenten	2001	0.6
Capita Selecta uit de kinderpsychiatrie	2001	3.6
Psychodiagnostiek voor kinderen van 7-12 jaar	2002	1.5
Kinderspel RINO	2002	0.5
Basiscursus gedragstherapie	2003	3.6
Specific courses		
Klinische neuropsychologie bij kinderen	2000	2.6
Klinische neuropsychologie bij volwassenen	2000	2.6
Neurotraining	2000	2.6
Psychologische patiëntenzorg in de oncologie	2004	1.8
EPNS training course	2005	0.7
Seminars and workshops		
Eisai studie workshop	2008	1.0
KNOP	2002, 2012	0.3
SKION dagen	2010,2012	0.6
NVKN	2004, 2009	0.4

(Inter)national presentations		
EPNS	1999, 2005	2.0
Geheugencongres SIG	2000	1.0
KOCR congres	2004	1.0
NVN (Neuropsychologie)	2004	1.0
NVK congres	2007, 2011	2.0
(Inter)national conferences		
EMCO Diagnostiek van angststoornissen	2001	0.3
EMCO Niet aangeboren Hersenletsel	2002	0.3
NVN (Neuropsychologie)	2001, 2002, 2003, 2004 (2x), 2006, 2007 (2x)	2.1
PAZ internetcongres	2010	0.3
SCEM congres Neuropsychologie en tekens	2010	0.3
Hogrefe Executieve funties in de praktijk	2010	0.3
Samen nog Beter 3	2011	0.6
NIP Specialist online	2011	0.5
Lecturing		
Klinische les 1 Noord	2000, 2002	0.5
Najaarsvergadering NVKN	2004, 2009	1.0
Nascholing kinderartsenweek	2006, 2007	1.0
Diagnostiekwerkgroep Kinder- en Jeugdpsychiatrie	2007	0.5
Neuropsychologie binnen de GZ-opleiding, RINO Utrecht	2008-2012	4.2
Vakgroep psychologen	2010	0.5
Minor Kinderoncologie, EUR	2010, 2011, 2012	1.5
SKION dagen	2012	0.5
KNOP	2012	0.3
Supervising		
Supervisie stage master studenten neuropsychologie	1999-2012	22
Supervisie Master's thesis	2000-2012	5.1