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Cognitive functions in children with myelomeningocele without hydrocephalus

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Abstract
Objective The aim of this study was to explore the separate effects of myelomeningocele (MMC) and hydrocephalus on intelligence and neuropsychological functions in a population-based series of children.
Material and methods Of the 69 children with MMC born in 1992–1999 in western Sweden, nine did not develop hydrocephalus. Eight of them participated in this study and were compared with age- and gender-matched children with MMC in combination with hydrocephalus and with controls.
Results Children with only MMC had an IQ of 103 compared with 75 in those with hydrocephalus added to the MMC and they had significantly better immediate and long-term memory and executive functions. When compared with controls, they had difficulty with learning and executive functions, but when the two children with an IQ of <70 were excluded, those with only MMC performed just as well as the controls.
Conclusion Hydrocephalus rather than MMC in itself appeared to cause the cognitive deficits found in children with MMC.

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Introduction

Myelomeningocele (MMC) is a disabling congenital defect in which the neural tube fails to close completely during the first weeks of foetal development. Internationally, the reported live birth prevalence of MMC varies from 0.7 per 10,000 in the Czech Republic to 11.5 in Mexico [7]. In Sweden, there has been a decrease in the prevalence in recent decades from about eight per 10,000 live births in the 1970s to the present prevalence of 2.2 per 10,000.

The early closure defect, with destruction of the medulla and spinal nerves, results in difficulty with ambulation, bladder and bowel control, as well as fine motor function [26]. The neural tube defect may be associated with anomalies of the corpus callosum and the midbrain/tectum [9] and more than 80% of the children have an associated Arnold–Chiari malformation of the cerebellum and the hindbrain that blocks the cerebrospinal fluid flow which leads to hydrocephalus.

The developmental and functional characteristics of children with MMC have been studied since the 1960s [21, 33, 34] and we now have considerable knowledge of the physical, neural and cognitive phenotypes [18]. As a group, these children have a low average IQ with the characteristic relatively intact verbal functions in relation to visuoperceptual skills [10, 23, 37]. These relatively intact verbal skills as measured with IQ tests relate to things such as single-word knowledge but not other important language domains such as word retrieval, discourse and the flexible use of language, which may cause major difficulties for the children [3–5, 11, 15].

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Neuropsychological research has mainly focused on children with MMC in combination with hydrocephalus, as this combination is the most common. Due to the fact that there are relatively few children with MMC without hydrocephalus, it has been difficult to obtain reliable data on the effect of the MMC malformation in itself on IQ results and other cognitive functions. However, there are two studies that found a significantly lower IQ in children with MMC combined with hydrocephalus than in those with only MMC [31, 33]. In other studies, small not statistically significant differences have been found between the two groups [25, 32]. Even fewer studies have been performed in order to explore learning and memory functions and executive abilities in children with MMC without hydrocephalus. When verbal learning and memory in children with MMC with and without hydrocephalus were compared with controls by Yeates et al. [38], those with hydrocephalus were found to have significant retrieval problems, whilst those with only MMC did not differ from controls.

In another study [31], children with MMC combined with hydrocephalus performed poorly in both verbal and non-verbal memory tests when compared with those without hydrocephalus and Fletcher et al. [17] reported that children with MMC without hydrocephalus performed significantly better than those with hydrocephalus in tests of executive functions.

The aim of this study was to examine verbal and visuospatial learning, memory and executive abilities in children with MMC without hydrocephalus and to compare them with children with MMC combined with hydrocephalus, as well as with normal controls, with the aim of exploring the role of hydrocephalus in the complex pattern of cognitive impairments in children with MMC. Another objective was to investigate whether MMC in itself was associated with cognitive deficits.

Materials and methods

Participants

Between 1992 and 1999, there were 69 children with MMC amongst the 188,998 children born in western Sweden, i.e. a live birth prevalence of 3.5 per 10,000 in this population-based series. Nine children (15%) did not develop hydrocephalus, corresponding to a prevalence of MMC without hydrocephalus of 0.5 per 10,000 live births. By the time of the examination, one child had moved out of the country and the study group therefore comprised of eight children aged 8–13 years (mean age 10.5), five boys and three girls. They were matched at group level for age and gender with eight children with MMC and hydrocephalus (mean age 11.2), five boys and three girls, and eight controls (mean age 10.7), five boys and three girls.

The normal controls were selected from mainstream schools and were considered to be of average intelligence. The inclusion criterion for children with hydrocephalus was an IQ of at least 70, whereas all the children with only MMC were included.

Instruments

Intelligence The children with MMC and hydrocephalus were tested using the Wechsler scales; two with Weschler Preschool and Primary Scale of Intelligence-Revised [35] and six with Wechsler Intelligence Scale for Children (WISC)-III [36]. The eight children with MMC without hydrocephalus were all tested with the 1992 version of WISC-III.

Neuropsychological functions The instrument that was used was a Swedish translation of a neuropsychological test battery for children 7 to 14 years of age, the "Neuropsychological assessment of the school-aged child" (NIMES) [2], comprising ten tests of different neuropsychological functions in the domains of auditory-verbal and visuospatial learning and memory, plus executive abilities (Table 1).

Registration skills (immediate memory) were assessed with the visuospatial Corsi block test [24], where the child was asked to tap blocks in sequences of increasing lengths, and the auditory-verbal Digit span test [36], where the task was to repeat series of digits of increasing length.

Verbal learning and memory was assessed with the Rey Auditory Verbal Learning Test [28], where the child has five attempts to listen to and learn as many words as possible, and Story Recall [1, 8], where the child listens to two short stories and then tries to recall them correctly.

Spatial learning and memory was assessed with the Spatial Learning Test [1, 22]. The children were asked to memorise and recall the positions of nine pictures on a wooden board. Another spatial learning and memory task involved copying a complex figure (the complex figure of Rey) [27] and then drawing it spontaneously without looking at the original. This is also a measure of visuoconstructional ability.

Long-term memory for auditory-verbal and visuospatial material was measured by asking the children to recall the word list and the stories after 30 min, to place the pictures and draw the complex figure of Rey as correctly as possible.

Four tests assessed the visual executive functions of planning and problem solving: the Trail Making Test A and B [30], where the children were asked to draw lines between numbers and letters as quickly as possible, an evaluation of the child's organisational ability when

Table 1 Tests in the neuropsychological assessment of the school-aged child (NIMES) measuring auditory-verbal and visuospatial registration skills, memory and the executive functions of problem-solving and planning and organisation

Functions	Auditory-verbal	Visuospatial
Registration skills	Digit span	Block span
Short-term memory	Story recall	Complex figure of Rey
		Recall
Learning	Rey auditory-verbal learning test	Spatial learning test
Long-term memory	Story recall	Complex figure of Rey
	Delayed recall	Delayed recall
	Rey auditory-verbal learning test	Spatial learning
	Delayed recall	Delayed recall
Problem-solving		Tower of London
Planning and organisation	Verbal fluency test	Trail making test
		Complex figure of Rey

drawing the complex figure of Rey and the problem-solving task of the Tower of London Test [29]. In the Tower of London Test, the children were asked to change the position of three wooden balls on sticks, similar to models presented on 12 cards, in a prescribed number of moves. The solution time was also measured in this test. Aspects of language executive function were measured with the Verbal Fluency Test [19], where the children were asked to find as many words as possible in 1 min, beginning with F, A and S, respectively.

Scoring of data and statistical analysis

All raw scores were converted to standard scores, i.e. *T* scores, where 50 is the mean (standard deviation (SD) 10). *T* scores of ≤20 (i.e. −3 SD) were set at 20. Group differences in subtests, functions and domains from the NIMES were analysed with the Kruskal–Wallis analysis of variance and followed up with the Mann–Whitney *U* test to reveal differences between pairs of groups. The five functions and the two domains comprise mean composite *T* scores for the subtests included (Table 2).

Ethics

The study was approved by the Research Ethics Committee at Gothenburg University. Informed consent was given by all the children and their parents.

Results

Intelligence

There was no statistical difference in full-scale IQ between the children with MMC and hydrocephalus (median IQ 75; range 71–81) and the children with MMC without hydrocephalus (median IQ 103; range 46–109; $p=0.11$). No difference was found between verbal and performance IQ (median verbal IQ=100, performance IQ=99) in the group with MMC only, whereas there was a significant difference between the verbal IQ of 85 and the performance IQ of 70 ($p<0.05$) in the group with MMC and hydrocephalus.

Neuropsychological functions

Children with MMC without hydrocephalus compared with children with MMC and hydrocephalus When comparing all eight children with MMC without hydrocephalus, including the two children with an IQ of <70, with the children with MMC and hydrocephalus, the children with hydrocephalus performed significantly more poorly on the functions of registration skills (immediate memory; $p<0.05$), long-term memory ($p<0.05$) and executive functions ($p<0.01$). The children without hydrocephalus obtained fairly normal results according to standard test norms, whilst the children with MMC and hydrocephalus achieved results 1–2 SD below norms.

For registration skills, the difference was significant in the visuospatial Corsi block subtest, for long-term memory in both the visuospatial and auditory-verbal subtests and for executive functions in all four subtests of visuospatial planning and organisation. The functions and subtests of learning and short-term memory did not reveal significant differences between the groups, apart from the fact that the children with MMC and hydrocephalus performed more poorly in the sub-test of visual short-term memory ($p=0.05$) and in the visuospatial domain ($p=0.05$) but not in the auditory-verbal domain.

When the two children with an IQ of <70 were excluded from the group with only MMC, this group significantly exceeded those with MMC and hydrocephalus in all functions and in the majority of the subtests, as well as in the auditory-verbal and visuospatial domain (Table 3). Only in the three tests of spatial learning, the Tower of London

Table 2 Medians and range of *T* scores in 15 tests from NIMES portioned into five neuropsychological functions for eight children with MMC without HC, eight children with MMC and HC and eight controls

Functions and subtests	MMC (n=8)		MMC+HC (n=8)		Controls (n=8)		p
	Median	Range	Median	Range	Median	Range	
Registration skills	45	36–58	38	27–48	45	36–51	<0.05
Corsi block	47	42–57	42	32–48	46	37–58	<0.05
Digit span	45	30–58	38	21–47	46	30–54	ns
Short-term memory	49	20–57	32	27–42	56	41–67	<0.01
ROCF recall	45	20–65	31	20–44	60	42–77	<0.01
Story recall	50	20–63	32	20–57	54	39–68	<0.05
Learning	53	20–58	42	30–54	55	45–72	<0.01
Spatial learning	54	20–70	50	37–65	62	55–69	<0.05
RAVL 1–5	47	20–60	33	20–43	52	20–75	<0.05
Long-term memory	51	22–57	33	23–46	51	34–65	<0.01
Spatial learning delayed recall	58	20–60	42	20–58	47	25–60	ns
ROCF delayed recall	36	24–61	30	20–52	60	36–73	<0.01
Story delayed recall	46	20–62	30	20–42	50	36–60	<0.05
RAVL delayed recall	52	24–66	32	20–52	57	38–71	<0.05
Executive functions	50	31–55	36	26–40	54	48–65	<0.001
Trail Making Test A	54	20–71	33	20–48	52	41–58	<0.01
Trail Making Test B	53	20–59	37	20–49	53	43–64	<0.05
ROCF organisation	46	23–57	37	20–45	65	49–77	<0.001
Tower of London	50	33–80	34	20–50	60	51–70	<0.01
Verbal fluency	41	33–57	40	27–52	50	31–70	ns

MMC myelomeningocele, *HC* hydrocephalus, *ns* not significant

and verbal fluency did the groups not differ significantly. The median *T* scores did not differ very much, at most 1 SD (in two sub-tests of long-term memory), but the ranges were generally much narrower in the MMC group.

Children with MMC without hydrocephalus compared with controls The eight children with MMC performed significantly more poorly than the controls in terms of learning (p<0.05), executive abilities (p<0.05) and in the visuospatial domain (p<0.05). No differences were noted for short- or long-term memory or for the auditory-verbal domain. When the two children with an IQ of <70 were excluded, there were no differences between the groups, apart from the two visuospatial subtests, spatial delayed recall (p<0.05) and the executive organisation of drawing the Rey complex figure (p<0.05).

Table 3 Medians and ranges in auditory-verbal and visuospatial domains of neuropsychological functions in six non-learning-disabled children with MMC without HC and eight children with MMC and HC

Domains	MMC (n=6)		MMC+HC (n=8)		p
	Median	Range	Median	Range	
Auditory-verbal	52	42–55	34	29–46	<0.001
Visuospatial	52	48–55	37	26–43	<0.001

MMC myelomeningocele, *HC* hydrocephalus

Children with MMC without hydrocephalus and children with MMC and hydrocephalus compared with controls When comparing the three groups, children with MMC only, children with MMC in combination with hydrocephalus and controls, a main effect of group was found for all neuropsychological functions (Table 2).

Registration skills The children with only MMC performed as well as controls in both the Corsi block test and the Digit span, even if the results were slightly under the standard norm. The children with hydrocephalus achieved results 1–1.5 SD below the norm and there was a significant difference between children with hydrocephalus and controls in the Corsi block test (p<0.01) but not on Digit span.

Short-term memory There was a significant difference between the two clinical groups and controls in terms of short-term memory (p<0.01). The greatest difference was found for visual short-term memory, where controls performed almost 1 SD over the standard norm, whereas children with MMC and hydrocephalus performed 2 SD below.

Learning Visuospatial and auditory-verbal learning tests revealed significant differences (p<0.05) between both MMC groups and the controls, who exceeded the norms by 1 SD in the visuospatial learning test and the Rey auditory verbal learning test.

Table 4 Medians and ranges in auditory-verbal and visuospatial domains of neuropsychological functions in eight children with MMC without HC, eight children with MMC and HC and eight controls

Domains	MMC (n=8)		MMC+HC (n=8)		Controls (n=8)		p
	Median	Range	Median	Range	Median	Range	
Auditory-verbal	51	30–55	34	30–46	51	40–62	≤0.01
Visuospatial	51	31–55	37	26–43	57	47–59	<0.001

MMC myelomeningocele, *HC* hydrocephalus

Long-term memory The difference between the groups was significant for long-term memory (p<0.01), but in one of the four tests comprised in this function, spatial delayed recall, the three groups performed fairly equally and no significant difference was found. The recall of the visuoconstructional material of Rey revealed the greatest difference. The children with only MMC scored below the norms by 1 SD and the children with hydrocephalus by 2 SD, compared with the controls that exceeded the norms by almost 1 SD.

Executive functions When comparing the three groups, the differences were significant (p<0.001), except in the verbal fluency test, where the difference between the clinical groups and controls was not significant. When comparing the two domains of auditory-verbal and visuospatial functions, the differences were significant for both domains, p=0.01 and p<0.001, respectively (Table 4).

When the two clinical groups were compared with the controls, it was evident that children with MMC combined with hydrocephalus were those who mainly contributed to the group differences. The children with MMC in combination with hydrocephalus differed significantly in all five functions that were tested compared with controls (registration skills, p=0.01; short-term memory, p<0.001; learning, p<0.001; long-term memory, p<0.05; executive functions, p<0.001). Children with only MMC differed significantly from controls, but to a lesser extent than those with hydrocephalus, on learning (p=0.05) and executive functions (p<0.05), respectively, but not regarding registration skills or short- or long-term memory. After excluding the two children with an IQ of <70, they performed as well as the controls (Fig. 1).

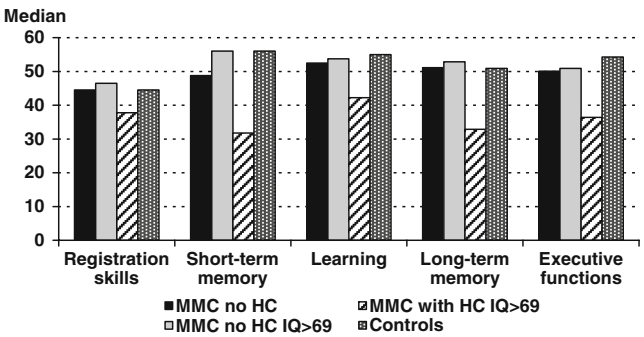

Fig.1 Medians of five neuropsychological functions for eight children with myelomeningocele (*MMC*) without hydrocephalus (*HC*), six children with myelomeningocele without hydrocephalus and an IQ of ≥70, eight children with myelomeningocele and hydrocephalus and eight controls

Discussion

The rarity of children with MMC not associated with hydrocephalus makes it difficult to explore cognitive and other neuropsychological functions in population-based, i.e. representative, cohorts. However, despite the small number and overlapping abilities, it should be possible, by careful matching and by using non-parametric statistics, to obtain an indication of whether MMC in itself is associated with cognitive deficits and to assess the added effect of hydrocephalus on cognitive development.

In this study, the children with only MMC performed significantly better than those with MMC in combination with hydrocephalus on registration skills, long-term memory and executive functions and after excluding the two children with an IQ of <70, the differences were significant for all neuropsychological functions and for both the auditory-verbal and the visuospatial domains.

The children with only MMC differed significantly from controls in terms of learning and executive abilities and in the visuospatial domain, but when the two children with an IQ of <70 were excluded, there were no differences in any neuropsychological function or domain between children with MMC and controls. This suggests that MMC alone is not a major determinant of neuropsychological impairments. However, the two children with MMC and an IQ of <70 illustrate that there is also great variability in children with MMC without hydrocephalus when it comes to cognitive outcome.

The neural phenotype in MMC is due to a nervous system abnormality which affects the spinal cord, the cerebellum, the brainstem and the corpus callosum. This abnormality may cause deficits of timing, attention orien-

tation and movement, deficits that are common in children with MMC. Timing deficits are closely linked to cerebellar abnormalities and may lead to problems with motor control and movement coordination, as in eye-hand tasks, such as throwing a ball and writing by hand. Attention orientation, both overtly with eye movements and covertly, in shifting attention, is related to characteristic mid-brain malformations in children with MMC [13, 14]. It was shown by Fletcher et al. [18] that the core deficits are relatively independent, but the synchrony of core processes is important for many skills.

Dennis et al. [15] described a model of how the neural phenotype in MMC results in deficits with an impact on associative and assembled processing, which may lead to the characteristic cognitive MMC phenotype. Associative processing is based on the formation of associations, categorisations, enhancement and engagement, e.g. recognising faces or familiar words. Assembled processing requires the assembly of input across various content domains, such as understanding the meaning of a text or making mental perceptual rotations. Both assembled and associative processing are related to the core deficits in MMC, but the secondary CNS insult of hydrocephalus has an additional impact in moderating the assembled processing, by stretching axons and thinning cortical structures. Children with MMC with and without hydrocephalus are perceptually relatively strong in recognising objects and faces (associative) but have difficulty with figure-ground tasks and identifying moving objects (assembling) [12]. In memory tasks, the children with MMC and hydrocephalus have an intact implicit (associative) memory, which involves the ability to recall without the intention of remembering, but difficulty with explicit (assembled processing) memory, which requires a conscious effort to store and recall [39]. The perceptual difficulties are related to posterior cortex thinning [10, 17], but the neural correlates to the memory difficulties have not been identified.

In the present study, the children with MMC and hydrocephalus displayed significant difficulty in all the neuropsychological functions when compared with controls, reflecting deficits in both assembled and associative processes. The children with MMC but no hydrocephalus differed from controls in terms of the functions of learning and executive abilities. These functions are sensitive to intelligence and, when the children with learning disabilities were excluded the MMC group, did not differ from the controls. It is therefore possible to argue that children with MMC without the additional CNS insult of hydrocephalus may have normal associative and assembled processing, as measured by the neuropsychological tests used in this study.

Our findings were in agreement with earlier reports on MMC [17, 31, 33, 38], revealing a lower IQ, more memory and retrieval problems and more impaired executive functions in children with hydrocephalus added to the MMC. Iddon et al. [20] compared the neuropsychological profiles of young adults with MMC with and without hydrocephalus with controls and found the same pattern; individuals with only MMC had relatively unaffected cognitive functions and achieved test results within the average range or above, whilst those with MMC and hydrocephalus were significantly impaired in the vast majority of all the test scores.

MMC, with or without hydrocephalus, is a disabling condition where the children face problems with mobility and impaired bladder and bowel functions that influence their ability to participate. In addition, they run the risk of low self-esteem. The additional impairment of hydrocephalus adds considerable cognitive difficulties. Attempts to minimise the consequences of MMC by foetal surgery have not been promising in terms of the consequences of the spinal lesion, but they have reduced the incidence of hydrocephalus in these children [6, 16]. The finding in this study that hydrocephalus is the main cause of cognitive dysfunction in children with MMC supports the need for the further development of such methods for the prevention of hydrocephalus.

This study concludes that the small group of children with MMC without hydrocephalus may have normal cognitive functions, without the characteristic discrepancy between verbal and performance IQ often found in children with hydrocephalus added to the MMC and without the more specific neuropsychological deficits in learning, memory and executive functions often found in these children. The cognitive outcome therefore appears to be dependent on the additive and associated brain abnormalities, such as hydrocephalus, rather than being the consequence of the MMC malformation itself.

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