Neuropsychological outcome following childhood stroke- A review

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ABSTRACT

Objectives. Childhood stroke is a rare but devastating occurrence. Its infrequency has meant that a clear body of knowledge has not been fully established regarding its impact on neuropsychological outcome. Our aims were i) to critically review the recent literature on neuropsychological outcome following childhood stroke; ii) to investigate the factors related to neuropsychological outcome following childhood stroke.

Methods. Literature searches were conducted and revealed 39 relevant papers from the period 1999- 2015.

Results. The review found that a significant number of children experience difficulties in a wide range of neuropsychological domains, with particular vulnerabilities noted in attention, speed of information processing and executive functioning. There were inconsistent findings regarding the correlates of neuropsychological outcome, which is likely due to methodological limitations of the studies.

Conclusions. This review strongly indicates that childhood stroke can affect a myriad of neuropsychological domains, with attention, speed of processing and executive function particularly vulnerable. Methodological issues, particularly around heterogeneous samples and measurement difficulties, limit the conclusions that can be drawn regarding the predictors of outcome.

Keywords: Childhood Stroke; Neuropsychological Outcome; Review

INTRODUCTION

Stroke in childhood is a rare but nonetheless devastating occurrence. Perinatal stroke is defined as cerebrovascular events that occur between 28 weeks of gestation and 28 days of life, whereas childhood stroke includes cerebrovascular events that occur from 29 days of life up to 18 years of age [1]. Incidence rates vary between 1.3- 13.0 per 100,000, depending on inclusion criteria and methodology used [2, 3, 4]. Stroke is among the top ten causes of childhood death, with a mortality rate of 3.1 per 100,000 in children under one year [5]. Childhood stroke is more common in boys than girls (approximately 1.5: 1), regardless of age, stroke subtype or history of trauma [6, 7]. The well-documented lateralised linguistic, cognitive and emotional differences reported following left and right hemisphere stroke in adulthood are not as clearly defined following childhood stroke [8]. Arterial Ischaemic Stroke (AIS) accounts for approximately half of all strokes in children and occurs due to obstruction of an artery as a result of a clot, causing an interruption to blood flow, leading to infarction. Haemorhagic stroke is the result of bleeding from an arterial rupture. Variations in the aetiology, lesion location and volume can lead to a diverse range of physical, cognitive and functional impairments [85]. There is ongoing debate around the plasticity or vulnerability of the developing brain following early brain injury, such as stroke [9, 10].

Historically, there have been theoretical (e.g. the Kennard Effect) [11] and anecdotal assumptions that children generally have a better recovery than adults post- stroke. However, recent evidence suggests that children do not necessarily recover better than adults [12]. It is suggested that the long-term difficulties experienced by children following a stroke are not confined to neurological, physical and functional domains but are more wide-ranging [13, 14, 12]. An important difference between stroke in children and adults is the altered trajectory to achieve functional skills among children, versus often permanent loss of functional skills

among adults [15]. Furthermore, the extent and severity of difficulties may not become apparent immediately after stroke, according to the "growing into deficit" model, in which vulnerabilities may emerge as a child's environment becomes more demanding [15].

There is a significant dearth in research around cognitive outcomes following stroke in childhood. Many of the existing studies of cognitive and behavioural functioning are confined to samples of children who have had perinatal stroke [16, 17, 18, 19]. Infants who suffer a stroke perinatally offer valuable insights into aspects of plasticity or vulnerability of the developing brain following very early injury. These studies show that children with perinatal stroke may be at an increased risk for disabilities, relative to those who experience stroke later in childhood. This includes increased risk of developmental delay and epilepsy, as well as poorer cognitive and behavioural outcome [9, 19]. Other factors, including presence of seizures, lesion location and age at stroke onset, have also been shown to have deleterious effects on cognitive outcome (for reviews of earlier studies see [20, 21, 22].

Although there is evidence to indicate that outcomes may impact children who experience perinatal and childhood differently [9, 19], there are indications that stroke during childhood can also lead to long-term disabilities, affecting a wide range of domains in children and adolescents [12, 13, 14]. There has been emerging research interest over the past decade into the broader impact of stroke on a child's cognition and well-being. Hence, the aim of this review was to critically examine the recent existing literature on neuropsychological outcome following stroke during childhood.

The research questions were:

1) Does having a stroke during childhood lead to poorer performance across a range of neuropsychological domains than typical development?

2) What factors are related to neuropsychological outcome following stroke during childhood?

METHOD

Literature searches were conducted using Pubmedand PsychInfo (1999-2015) databases using the key words "childhood" or "p(a)ediatric"; "stroke" or "cerebral infarction"; and "outcome" with each of the following terms: "neuropsychological", "cognitive", "intelligence", "IQ", "behavio(u)r". The references of each article were also hand-searched and reviewed for relevant papers.

Papers were identified in the English language, which included children with stroke onset outside of the perinatal period and that had used objective measures (questionnaires and cognitive assessments) of function, behaviour, and neuropsychological assessment. Papers that exclusively recruited children with perinatal stroke were not included, as studies indicate that perinatal stroke may have a different trajectory developmentally to childhood stroke [9, 19]. Papers of early focal brain injury with heterogeneous aetiologies that included traumatic brain injury, dysplasia or malformations were also excluded. In total, 39 papers were included in the review.

RESULTS

Table 1 gives a brief summary of each study, outlining the main findings and factors associated with outcome. The studies reviewed were heterogeneous in terms of design and measures used. There was significant within and between subject variation in terms of age range at stroke onset (pre-natal to 17 years and 7 months), and at assessment (infant period to young adulthood), and stroke type. Inclusion criteria varied in terms of recurrent stroke and syndromes (such as moyamoya or sickle cell disease) but many studies did not clarify whether these groups were included.

The majority of studies (n= 33) were cross-sectional in design. Many studies (n= 21) did not recruit a control group but compared scores to published normative data. The sample sizes ranged from a case series with five participants with stroke [49],) to a large prospective longitudinal outcome study of 163 children with a history of stroke (ischaemic and sinovenous thrombosis) [23]. Due to small sample sizes, several studies report predominantly descriptive findings with limited statistical analysis.

Neuropsychological Outcome

General Intellect. In total, 26 of the studies reviewed reported general intellectual outcome using standardised measures of intellectual function. All studies used the age-appropriate Wechsler Scales: Wechsler Intelligence Scale for Children Third/ Fourth editions: WISC III/IV [60, 63], Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) [62] and Wechsler Abbreviated Scale of Intelligence (WASI) [61] or their foreign language equivalent. The Bayley Scales of Infant Development (BSID-II) [64] were included in five studies to assess general development in infants and toddlers below preschool ages. Where scores were reported, mean full scale IQ was generally at the lower end of the average range [58, 34, 47] or in the low average range [42]. Wide variation in full scale IQ was reported in all studies (e.g. Range full scale IQ= 65- 116 [55]; Range full scale IQ = 52-132 [39]).

In studies where a control comparison group was included, children with stroke consistently performed significantly lower on full scale IQ, verbal IQ and performance IQ than orthopaedic controls [38, 42], healthy siblings [54] and children with sickle cell disease with no evidence of stroke [54]. There were non-significant trends towards poorer performance between children with stroke and asthma controls in a recent study [34]. One study showed that full scale IQ and performance IQ, but not verbal IQ, was significantly impaired for children with sickle cell disease and stroke compared with children with sickle cell disease and no evidence of stroke [26]. Comparisons with theoretical population norms (M= 100, SD= 15) were used in studies when control groups were not included. The majority of studies found that children's scores on full scale IQ and index measures were significantly lower than the normative population means [58, 31, 14, 33, 34, 47]. Performance IQ but not verbal IQ was significantly

lower than the population mean in one study [21]. Another study did not find a significant difference in full scale IQ compared to population norms [57].

Specific differences between verbal IQ and performance IQ were reported in three studies. Two studies found significantly higher verbal IQ than performance IQ [48, 31]. A third study found a significant difference between verbal IQ and performance IQ for 12/18 participants [14]. Of those, 7/12 (58%) had higher verbal IQ than performance IQ, whereas 5/12 (42%) showed the opposite pattern, with performance IQ significantly higher than verbal IQ. No significant differences were found between verbal and nonverbal abilities in other research [45].

Academic Attainment and Impact on Education. Few studies specifically assessed academic attainments. Max's series of studies with a group of children with stroke (n= 29) used the abbreviated measure of attainments, the Wide Range Achievement Test- Revised (WRAT-R) [65] to assess reading, spelling and arithmetic. Compared with orthopaedic controls, the group with stroke as a whole had significantly lower scores on all three academic attainments, all of which were in the low average range (Reading: standard score = 80.8; Spelling: standard score = 84.5; Arithmetic: standard score = 81.6) [42, 44, 45]. Reading difficulties were assessed in a small case series (n= 5) of children with left hemisphere lesion strokes [49]. All five had impaired reading skills below what would be expected for their chronological age. Further assessment indicated that their impaired reading skills could be explained by different specific learning difficulties, such as dyslexia or a language deficit. Another study found that reading comprehension scores on the Wechsler Individual Attainment Test (WIAT-II) [66] for children with stroke were in the lower end of the average range and significantly lower than normative data [47]. Over half of the children in this study were receiving extra educational support in school. Several studies

highlighted the negative impact on education and schooling. 63% in one study were reported as experiencing school difficulties [32]. Between 19% [14] and 31% [56] of children were reported as attending special schools. Of those children attending mainstream schools, over half were reported in most studies to be receiving additional educational supports [30, 31, 14, 48, 56].

Language. The Clinical Evaluation of Language Fundamentals (CELF-R; CELF-III) [67, 68], a well-validated gold standard measure of expressive and receptive language, was used in four studies.

One study showed that of 15 children who were administered the CELF-R, the majority (73%) had average or above average range scores on the receptive domain. However, over half of the children (53%) had difficulties on the expressive language domain. In a case series of nine children presenting with aphasia after subcortical infarcts, although conversational speech and comprehension was considered within the normal range, expressive language difficulties (word finding, dysfluency and written language) were still evident in 6 of 9 children on standardised assessment [32]..

Another study found very few difficulties with pragmatics or conversational language [25]. Phonological (speech sounds) and syntactic (grammatical) impairments were found in 40.6% of their group and semantic difficulties were found in 34.4% children. Similar findings were reported in a group of children with left hemisphere lesions (n= 13) when compared with lesion-matched adults on ratings for narrative spontaneous discourse. The adults performed worse than the children in the domains of word-finding, fluency, paraphasic errors and auditory comprehension. All the children were rated as performing normally, with no impairment in spontaneous speech [8].

One study adopted a discourse story retell methodology in their research [29]. Children with stroke produced a greater number of lower level concrete interpretations, significantly shorter sentences and obtained lower scores in measures of information content and organisation than the orthopaedic control group.

Two control-matched studies found no significant differences between children with ischaemic stroke [27] and children with sickle cell disease and stroke [51] on expressive or receptive language measures. Of note, as the complexity of the task increased, the children with stroke maintained accuracy but required significantly more time to complete the task than controls [27].

Attention. Difficulties with attention, concentration and processing speed are reported in many (n=19) studies where objective neuropsychological measures were administered. Variability in response time, reflecting sustained attention difficulties, was identified in two studies [31,52]. The first study identified a slower response time among children with stroke compared to normative data [31]. A similar finding was also made by other researchers on a task of divided attention [27]. Several other studies also identified reduced speed of processing from more general index measures, such as lower scores on Freedom from Distractibility scale (WISC III) [60, 54] or from a significant proportion of children performing below the expected norms on particular subtests of processing speed [48].

Several studies from Max's research group investigated attention using different methodologies (experimental, behaviour questionnaires, clinical assessments) [41, 42, 43, 44, 45, 46]. Difficulties reflective of inattention and impaired alerting/ sensory-orienting attention were reported in addition to significantly longer reaction times [43, 44].

Two studies using the Test of Everyday Attention for Children (TEA-Ch) [69] as an outcome measure identified significant weaknesses among children with stroke on a response inhibition task [34, 47]. 50% of participants were classified as "Impaired" on this task [47]. Significant difficulties with divided attention, switching and sustained attention were also evident.

Memory. In studies where memory was assessed, the California Verbal Learning Test, Children's Version (CVLT-C) [70] was the most common measure administered. No significant differences in verbal learning between children with stroke and control groups were found in a number of studies [29, 31, 51].

Other researchers have found some subtle differences between children with stroke and controls on the CVLT-C. These findings indicated that children with stroke had a profile of relatively compromised encoding (learning fewer words), less efficient use of learning strategies (semantic clustering), less benefit from semantic cues (long delay cued recall), and diminished retrieval after a long delay (free and cued) [27, 38].

Other measures of memory have also shown varied results. Normally distributed scores were found in a study using the Wechsler Memory Scales (WMS) [71, 28]. The Rey Osterreith Complex Figure (ROCF) [72, 73] was sensitive to mild / moderate difficulties for both left hemisphere and right hemisphere groups [45] and in 6 of 10 children with stroke in another study [31]. Some vulnerability in visual memory recall was evident on the ROCF and Children's Memory Scales (CMS) [74, 24], which may be linked with visuospatial difficulties. Control-matched studies identified poorer functional memory [27] and poorer immediate memory performance [36, 37].

Visuospatial and Visuomotor Function. A limited number of studies administered specific objective measures of visuospatial and/or visuomotor function in neuropsychological assessments with children with stroke. Of those, four studies

identified significantly impaired performance on visual-motor integration [41], visual construction [8] and perceptual motor skills [31, 33]. Two studies identified nonsignificant trends towards lower scores on subtests measuring visuoconstructive skills [24, 57] and nondominant hand dexterity [24]. A study that addressed asymmetry in visuospatial processing indicated that visual search for the contralateral field was consistently disrupted across left hemisphere, right hemisphere and bilateral lesion groups [53]. However, only one study mentioned the impact of change in handedness as a factor in poorer visual spatial skills [8].

Executive Function. When attention is considered independently, few studies have investigated other executive function abilities following childhood stroke. In the studies that have investigated executive functions, poorer performance than would be expected from a normative distribution was identified for abstract reasoning and problem solving [30]. No significant differences were found on a card-sorting task, an adaptation of the Wisconsin Card Sorting Task (WCST) [75], between children with stroke and a healthy comparison group [30]. By contrast, another series of studies identified poorer performance on the WCST among children with stroke [44, 45, 46]. Children with stroke without symptoms of Attention Deficit Hyperactivity Disorder (ADHD) had scores in the average range on WCST measures. No significant differences were found in verbal fluency skills [44]. A third study that administered the WCST and the Tower of Hanoi identified poorer performance than sibling controls for correct responses on the Tower of Hanoi task [51].

More recently, studies have focussed more specifically on executive function abilities in children with stroke [39, 40, 47]. These studies used both objective neuropsychological measures of executive function (Delis Kaplan Executive Function System; DKEFS) [76] and measures of everyday executive function behaviour

(Behaviour Rating Inventory of Executive Function; BRIEF) [77]. Deficits in executive functioning were notable in attentional control, cognitive flexibility and information processing and in behavioural aspects of executive function [39, 40]. In another study, difficulties were highlighted with sequencing, switching, working memory, and cognitive flexibility [47]. As a group, performance was in the low average range and significantly lower than standardised norms. 30% of the sample were 'impaired' on these executive function tasks [47]. Parents and teachers also identified significant difficulties in the areas of behavioural regulation, metacognitive skills and global everyday executive function abilities.

Summary of Neuropsychological Outcome

This review indicates that few domains of neuropsychological functioning are unaffected following childhood stroke. When appropriate measures are used, clear vulnerabilities in attention, speed of processing and executive function difficulties exist. Subtle impairments in higher-level expressive language, memory and visuospatial abilities are also likely to be found. These impairments have a significant impact on general intellectual abilities and the acquisition of new information, affecting academic attainments and difficulties in school. Verbal abilities, particularly receptive language and conversational skills, appear to be better preserved.

Factors associated with neuropsychological and behavioural outcome

Age at stroke onset. Children whose stroke onset was not limited to the pre- or perinatal period were specifically examined in this review. Several studies investigated whether age at stroke onset had a significant impact on outcome. However,

methodological limitations complicate the findings, such as differing classification of 'early' versus 'late' onset stroke [46, 38, 21, 48, 58].

One study found that earlier age at stroke was associated with weaker cognitive performance overall, but this relationship was modulated by lesion location [58]. They found different periods of peak vulnerability for subcortical lesions (perinatal period) and cortical lesions (1 month to 5 years). Another study found that significant deficits lateralised to the right hemisphere (perceptual reasoning ability and processing speed) were found only in the early onset group [24].

Differences between an early onset group and matched controls were larger than the differences between the late onset group and matched controls across the domains of IQ, academic attainment, language, memory and visuospatial [46]. In contrast, findings relating to executive functioning indicated a greater vulnerability among the late onset group. However, as no direct early versus late comparisons were conducted, it is difficult to arrive at specific conclusions.

Another study directly compared the performance of early onset stroke vs. late onset stroke. They identified poorer performance on long delay free recall and recognition on the CVLT-C, a task of auditory short-term memory and trends towards significantly lower verbal IQ and performance IQ for the early onset groups [38]. Two studies identified better outcomes for strokes occurring in early/middle childhood compared to infant onset or later onset, including higher verbal reasoning and working memory [24] and visual-spatial reasoning [31]. However, these studies reported different age ranges; 5 to 10 years of age [31] and 1 to 6 years of age [24].

In many studies, early age at stroke onset was associated with poorer outcomes, including lower FSIQ [27], orienting attention [45], expressive and receptive language

skills [25, 24, 29, 32], verbal memory [46, 24], perceptual reasoning [24] and working memory [31].

In contrast, one study found that the late onset group in their study had lower verbal IQ and performance IQ than the early onset group [21]. These differences did not reach statistical difference, possibly due to small group sizes. Earlier age of stroke was associated with better performance on measures of executive function in another study [47]. Other researchers similarly did not find significant relationships between age at stroke onset and IQ [35]. No significant differences between perinatal and acquired hemiparesis groups were found [36]. Stroke in mid-childhood (5- 10 years) had the best outcome for IQ scores [48]. A similar pattern was found in another study, with stroke onset during middle childhood (5-9 years) associated with better performance IQ [31]. In contrast, other research did not find an association with age at stroke onset and expressive or receptive language scores [50].

Neurological factors: Lesion characteristics and seizure history.

A number of studies identified associations between larger lesion size and poorer cognitive outcome. One study showed that lesion volume (specifically the size of the rostral body of the corpus callosum) was a robust predictor of IQ, distractibility, speeded production and working memory [54]. Larger lesion size was associated with lower IQ [31, 34] slower processing speed [31], poorer spatial performance after controlling for lesion location [51], executive functioning [39] and accuracy on a visual attention task [45]. Three studies did not find lesion volume to be significantly associated with outcome [29, 43, 52].

Associations between left hemisphere lesions and lower scores on working memory, verbal memory and receptive language were found [24]. Left hemisphere lesions were also associated with below average vocabulary scores [30], general slowing of reaction

times and intact global and local processing relative to right hemisphere lesions [53]. Groups with right hemisphere lesions performed worse on attention measures, whereas the left hemisphere lesions performed worse on verbal domains [36]. One study identified significantly better performance among right hemisphere lesion group on all measures of a developmental neuropsychological assessment (NEPSY-II) [78, 37]. However, a number of studies did not find any associations between cognitive outcome and lateralisation [27, 38, 45, 8]. Another study also did not find an association between lesion laterality and IQ, with the exception of higher scores on processing speed for those with left-sided lesions than those with right-sided lesions [48].

Studies that examine lesion location, looking at anterior, posterior or specific areas, are limited by small sample sizes, broad categories of lesion location and heterogeneous sub-groups. Lesions involving both cortical and subcortical structures were associated with poorer inhibitory control [34], working memory [57], processing speed [57] and lower IQ scores [35, 57, 58]. This effect remained significant after partialling out lesion size in one study [58]. Children who had associated neurological disorders prior to stroke (e.g. head trauma, meningitis) had a significantly lower mean IQ than the population mean [35]. One study showed that children with subcortical lesions had a tendency towards better neurological prognosis than cortical lesions [56]. Children with lesions in the basal ganglia region were associated poorer attention [52] and performed more poorly than controls in another study, with no significant difference between left- and right hemisphere groups [50]. Other findings indicated that children with anterior, diffuse and posterior lesions had a differential profile compared to controls on a verbal working memory task [59]. However, very small numbers limit conclusive interpretations of these findings. Stroke involving both

frontal and extra-frontal regions impacted performance on executive function tasks in one study [40].

Many studies identified associations between the presence of epilepsy and poorer outcome across a number of cognitive domains, including general intellectual functioning [30], memory [36], speed of visual attention processing, executive functions, new learning for the perinatal group [37] and unspecified greater number of neuropsychological problems [56].

Sex. When specifically investigated, most studies reviewed did not find that a child's sex was associated with a particular outcome [42, 43, 44, 48, 58].

Specific sex differences were found for particular outcomes in two studies. One showed a trend towards lower FSIQ, VIQ and PIQ for boys [21]. Male sex was a significant risk factor for lower scores in the attention and verbal domains in a second study [36].

Other factors. Other factors investigated for association with outcome include medical factors, time since stroke, age at assessment, socio-economic status and stroke type (arterial ischaemic stroke, haemorrhagic, sinovenous thrombosis, idiopathic or symptomatic). In a group of children with sickle cell disease, having a history of either overt or silent strokes, severe chronic anaemia (hematocrit <20%), and high platelet count/thrombocytosis were independent factors of cognitive deficit (full scale IQ<75) [26].

Time since stroke was generally not found to be significantly associated with outcome [14, 45, 50]. Age at assessment was also not associated with outcome in many studies [42, 43, 44, 45]. Where associations were found, results were not necessarily consistent. One study found a trend for longer time since stroke (> 5 years since stroke) to be associated with better cognitive outcome [31].

Socioeconomic status was not significantly associated with outcome in one study [42]. However, other researchers found an association between higher IQ in children with stroke and higher socioeconomic status (professional parents) [35].

Findings with stroke type were also not consistent. One group did not find significant differences between children with arterial ischaemic stroke compared to sinovenous thrombosis on measures of IQ [35]. Another study also did not find a clear association between stroke type and outcome [46].

Summary of factors associated with outcome. Although several factors have been found to be associated with neurological and neuropsychological outcome, the findings remain inconclusive. In general, it appears the earlier age of stroke onset leads to greater vulnerabilities in language and functional disabilities. However, U-shaped trends, at least for particular skills such as executive function require further clarification. Greater lesion volume appears to lead to greater residual disability. However, the predictive power of lesion volume and other lesion characteristics for neuropsychological outcome remains unclear. Seizures and other medical factors may also be related but again findings are inconclusive.

DISCUSSION

Summary of findings. The current review indicates that childhood stroke can lead to a range of neuropsychological difficulties. Although IQ levels may remain in the lower end of the average or low average range, a greater proportion of children function towards the lower end of the normative distribution than would be expected in the general population. Academic attainments are also affected, with mean scores for reading and arithmetic falling in the low average range. Expressive and higher-level language functions may also be impacted. Specific findings indicate particular

vulnerabilities with speed of information processing, encoding, attention, cognitive flexibility, working memory, and other executive functions. Findings are inconsistent for memory and visuospatial domains but subtle deficits can occur. Several studies highlighted the real-world impact of neuropsychological impairments on children's education and schooling. Across studies, approximately half the children required extra educational help and, proportions attending special schools varied from 19% to 31%.

Risk factors. Findings from this review indicate that a proportion of children with stroke are impaired across a range of domains. There are some indications that earlier age of stroke onset may lead to greater vulnerabilities, particularly in functional disabilities and language skills. The largest population-based study of childhood arterial ischaemic stroke to date corroborates this, finding that 69% of children aged <1 year at time of stroke had a poor functional outcome, compared to 49% for older children [79]. There is an indication that combined cortical and subcortical lesions are associated with poorer cognitive outcome overall. Epilepsy and history of seizures may be related to greater cognitive impairment. In general, however, inconsistent findings about predictive factors mean that coherent conclusions cannot be established at this point and further research is clearly necessary. A recent review has identified the importance of considering interaction effects between factors associated with cognitive outcomes [80]. The review examined the determinants of cognitive outcomes of perinatal and childhood stroke, identifying interactions between age at stroke by lesion location, lesion characteristics by neurologic impairment, lesion volume by time since stroke, sex by lesion laterality and seizures by time since stroke. These findings indicate a promising direction for future research.

Clinical Implications. Most studies reviewed called for careful assessment of neuropsychological outcome in children who have experienced stroke as part of routine clinical practice. Subtle higher-level deficits in functioning may be undiagnosed, particularly in children with no or very mild evidence of neurological residual disabilities. Regular neuropsychological assessments have been recommended for all children with evidence of stroke [47, 57]. Reports that children may "grow into their deficits" point to the importance of regular neuropsychological reviews for identification of difficulties, particularly as more complex skills are required for academic and social functioning [27].

A detailed neuropsychological assessment following childhood stroke should include investigation of strengths and weaknesses across a wide range of domains, including general intellect, academic attainments, language, memory, attention, executive functions and visuospatial skills. There is an increasing evidence-base indicating that childhood stroke can lead to reduced quality of life [31, 81]. Psychosocial factors including behaviour, adaptive functioning and quality of life should also be assessed in the context of a developmental perspective [81, 82]. Objective, standardised measures should be administered to the child, their parents and to their teachers to ensure multiple perspectives are considered [39, 40, 47, 81]. These assessments should lead to careful development of tailored interventions for the child and family and guidance for teachers, to maximise learning, independence and quality of life. They are essential to identify vulnerable children and families in need of further support. Recent findings highlight the importance of environmental modifications and responsiveness to the needs of children and their families, over and above attempts to modify the child through cognitive training [83]. For example, the significant impact

of family functioning and parental mental health on psychosocial outcome following childhood stroke has been identified in recent studies [84, 85].

The findings from this review also question clinical lore that children have 'better' outcomes than adults. Only one study reviewed directly compared lesion matched children and adults. They concluded that there was a high degree of similarity between ongoing impairments in neuropsychological and social function [8]. While lateralisation effects are not as clear in children as they are in adults with unilateral stroke, the overall findings from this review indicate that significant and persistent neuropsychological difficulties are present for between half and three-quarters of the children with stroke. There has been limited research investigating the impact of these difficulties into adulthood. High levels of depression have been reported among adult paediatric stroke survivors, indicating an important area for future research [86]. It is also important to highlight that the group of children (between a quarter and a half) *without* neuropsychological and psychosocial difficulties evident also deserve acknowledgement. Biopsychosocial resiliency and protective factors may be relevant and worthy of further study.

Methodological Limitations. The last decade has seen a developing interest in a spectrum of outcome factors outside of crude 'good' or 'poor' outcome classifications based on broad measures of neurological severity. This burgeoning research area is vital to inform clinical assessments and interventions. However, significant methodological considerations dominate the reviewed literature, many of them common to research in other rare paediatric populations.

Study Design. The vast majority of studies in this review were cross-sectional in design. This design has several advantages, particularly with rare populations, such as childhood stroke. However, causality cannot be established conclusively. For

example, due to the very nature of the sudden onset of childhood stroke, baseline assessments are not possible for the majority of children. The exceptions to this are children with identified risk factors or syndromes that increase their risk of stroke, such as moyamoya or sickle cell disease. Only three studies had designs that were prospective in nature, which allow for greater clarity around related causal factors.

Twenty studies did not use a control group in their design but compared their data to normative population means, where available. A variety of healthy community samples, sibling and medical controls were recruited when control groups were used. Although matched for environmental and SES factors, sibling controls may not be matched on age and sex factors. Medical controls, such as children with sickle cell disease, allow for matching of factors related to chronic health conditions. However, SCD itself may be associated with subtle cognitive effects, even for children without stroke [53].

Heterogeneity. Within-group and between-group variability is likely to have prevented firm conclusions being established. Studies reviewed included a mix of children with ischaemic, haemorrhagic and SVT stroke; age of stroke onset ranging from the prenatal period up to over 17 years; time since stroke ranged from months to 25 years. Unclear inclusion and exclusion criteria were also problematic in the studies reviewed. For example, not all studies clarified if children with recurrent stroke or medical conditions such as sickle cell disease were included.

Statistical Issues. Small sample sizes were very common in the 39 studies reviewed (10 of 39 (25%) studies <20 children with stroke; 23/39 (59%) studies <30 children with stroke; 32/39 (82%) <40 children with stroke). Smaller sample sizes leads to low power and a greater chance of type 2 errors. More descriptive findings were reported and statistical analyses was limited. Studies often reported within- group

comparisons, investigating factors based on lesion characteristics (left and right-sided lesions), age of stroke onset (early/late) or other medical and demographic variables. This led to subgroups with even smaller sample sizes. For example, one study compared working memory skills between children with anterior lesions (n= 4), posterior lesions (n= 4) and diffuse lesions (n= 12) [59].

Measurement Issues. A wide array of neuropsychological and behavioural measures was used in the studies reviewed. These included well-validated, commonly used standardised clinical measures, such as the Wechsler Scales. They also included unstandardised, experimental measures (visual search tasks) or questionnaires developed for the purpose of the study whose validity and reliability was not established.

Future Research. The findings from this review and the methodological limitations outlined point to several recommendations in terms of further research.

A range of neuropsychological difficulties was identified across studies. Reliance on the Wechsler scales of general intellect to assess subtle neuropsychological outcome has led to other cognitive domains being neglected in the research. These factors indicate strongly that a multidimensional assessment approach is necessary in future research that should include a wide array of well-validated and standardised neuropsychological assessments, known to be sensitive to vulnerabilities following childhood stroke. Using age-appropriate specific attention measures is recommended in order to identify the specific attention difficulties regularly experienced by children with stroke [39, 40, 47]. Future studies should include standardised clinical measures of attention [39, 40, 47, 51]. Further investigation into the wide-ranging impact of childhood stroke on executive function abilities is clearly warranted, using neuropsychological and behavioural measures [39, 40, 47].

Examining the impact of vulnerabilities in attention and executive function on academic, social and other areas of everyday life is warranted.

Assessment should also include objective, well-validated measures of psychosocial outcome including behaviour, mood, adaptive functional disability, preferably from multiple perspectives (child, parent and teacher).

Longitudinal studies are needed in order to monitor children with stroke at different transition points, including primary to secondary school and beyond to early adulthood. Findings from current limited studies indicate that functional status at one year poststroke strongly predicts outcome in adulthood [86].

Larger and more homogeneous sample sizes are clearly needed to increase the power of studies. Given the rarity of childhood stroke, it is likely that collaborative, multicentre studies with large databases are required.

Predictive risk factors, their interactions and interrelationships need to be identified in order to guide clinical assessment and intervention. Hypothesis-driven statistical analyses are needed to establish correlates of outcome. The relationship between neuropsychological factors, such as attention difficulties, and psychosocial factors, such as interpersonal issues, should also be examined.

As the last decade saw an increase in studies investigating outcome, research into efficacy of clinical interventions and support is now needed. This could include interventions found to be effective with other paediatric populations, such as Cognitive Behavioural Therapy (CBT) for mood difficulties, behavioural interventions, cognitive remediation, and school liaison.

Functional neuroimaging studies may help to elucidate many issues relating to vulnerability, plasticity and reorganisation of the developing brain following childhood stroke.

Conclusion

Childhood stroke is a rare but potentially devastating occurrence. Its infrequency has meant that a clear body of knowledge has not been established regarding its impact on neuropsychological outcome. This review indicates that a significant number of children with stroke experience long term difficulties in a wide range of cognitive areas, including general intellect, academic attainments, expressive language, abstract interpretations, visuospatial skills, attention, working memory, cognitive flexibility and emotional and behavioural regulation. Inconsistent findings regarding the correlates of outcome are likely to be due to methodological limitations of the studies reviewed. Methodological issues include limited prospective and longitudinal studies, lack of control groups, small sample sizes, measurement issues and heterogeneity of samples. Future research should address these methodological issues and in doing so, answer some of the many remaining questions regarding outcome following childhood stroke. This review strongly indicates that it is vital for children with stroke to be assessed clinically for neuropsychological difficulties and followed-up as necessary. Tailored interventions and support can then be developed in order to improve the quality of life of children who have experienced stroke during childhood.

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DECLARATIONS OF INTEREST

The authors report no conflict of interest.