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Systematic Review

Cognitive Functions in Children and Adults with Moyamoya Vasculopathy: A Systematic Review and Meta-Analysis

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Background and Purpose Patients with moyamoya vasculopathy (MMV) may experience cognitive impairment, but its reported frequency, severity, and nature vary. In a systematic review and meta-analysis, we aimed to assess the presence, severity, and nature of cognitive impairments in children and adults with MMV.

Methods We followed the MOOSE guidelines for meta-analysis and systematic reviews of observational studies. We searched Ovid Medline and Embase for studies published between January 1, 1969 and October 4, 2016. Independent reviewers extracted data for mean intelligence quotient (IQ) and standardized z-scores for cognitive tests, and determined percentages of children and adults with cognitive deficits, before and after conservative or surgical treatment. We explored associations between summary measures of study characteristics and cognitive impairments by linear regression analysis.

Results We included 17 studies (11 studies reporting on 281 children, six on 153 adults). In children, the median percentage with impaired cognition was 30% (range, 13% to 67%); median IQ was 98 (range, 71 to 107). Median z-score was −0.39 for memory, and −0.43 for processing speed. In adults, the median percentage with impaired cognition was 31% (range, 0% to 69%); median IQ was 95 (range, 94 to 99). Median z-scores of cognitive domains were between −0.9 and −0.4, with multiple domains being affected. We could not identify determinants of cognitive impairment.

Conclusions A large proportion of children and adults with MMV have cognitive impairment, with modest to large deficits across various cognitive domains. Further studies should investigate determinants of cognitive deficits and deterioration, and the influence of revascularization treatment on cognitive functioning.

Keywords Moyamoya disease; Intelligence; Child; Adult; Neuropsychological tests; Review

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Introduction

Moyamoya vasculopathy (MMV) is a cerebrovascular disorder of largely unknown etiology characterized by progressive stenosis or occlusion of the supraclinoid internal carotid arteries and their proximal branches.[1,2] Patients may present with transient ischemic attacks (TIAs) and ischemic stroke but also with headache, movement disorders, and seizures.[1,3] MMV can also lead to cognitive impairment.[4] Cognitive functions may not only be affected by overt or silent brain infarcts or hemorrhages but also by chronic hypoperfusion, as cognitive impairment has been diagnosed in adults with MMV without stroke.[5] Early age of onset and longer disease duration have been associated with the occurrence of cognitive impairment.[6] Many patients with MMV undergo surgical revascularization to improve cerebral blood flow (CBF) and prevent future ischemic stroke,[2] but prospective studies on the effect of surgical treatment on cognition are lacking. A previously published descriptive review has provided an overview on cognition in moyamoya disease (MMD) suggesting that the impact of MMV on cognition is more pronounced in children than in adults.[7] In the present study we systematically collected and meta-analyzed available quantitative information on the presence, severity and nature of cognitive impairment in children and adults with MMV and its determinants, in particular cerebral perfusion. Furthermore, we aimed to determine the effect of surgical intervention on cognition.

Methods

For the conduction of this systematic review we followed the meta-analysis of observational studies in epidemiology (MOOSE) guidelines.[8]

Search strategy and selection criteria

We searched Ovid Medline and Embase for publications of studies describing cognitive function in patients with MMV published between January 1, 1969 (the year the disorder was given its name) and October 4, 2016 (see online Supplementary for Syntax). No limits were set for languages; native speakers translated papers that were written in other languages than English, German, or French. Titles and abstracts were scanned and papers were included on the basis of full text by two authors independently (A.K. and C.J.M.K.); disagreement was resolved by consensus. Additional studies were included from the reference lists of included studies. We included studies reporting cognitive or intellectual functioning in children and adults that allowed analysis of quantitative data on group level (i.e., intelligence quotient [IQ] scores) of at least five patients. If authors reported neuropsychological assessment without providing raw neuropsychological data, we contacted them for additional data. In case of (suspected) overlap between study cohorts, we included the study with the largest sample size with information on the proportion of patients with impaired cognition. In case individual patient data were provided, we excluded patients without quantitative cognitive data.

Data extraction

Three authors (A.K. all papers; C.J.M.K. and E.B. half of the studies each) independently extracted data from selected papers. Disagreements were solved by consensus. Of the authors from 13 publications who were approached for additional data, one provided baseline characteristics and scores of neuropsychological tests,[9] five could not provide additional information, and seven authors did not respond. The risk of bias was evaluated by one author (A.K.) using the Newcastle-Ottawa scale adapted for cross-sectional studies (see online Supplementary for the Risk Assessment).[10]

We collected the following study characteristics: study design; midyear of study; in- and exclusion criteria; number of patients with MMD or moyamoya syndrome (MMS, known associated disease);[1] mean age and duration of symptoms (at time of diagnosis; presentation; neuropsychological assessment, operation, inclusion or not specified); proportion of females; ethnicity (Asian, Caucasian, Hispanic, African, and Afro-American, according to the definition provided by the authors, or—if not provided—by country of publication); site of clinical stroke or TIA (uni- or bilateral); application of diagnostic criteria for MMV;[1] site of vasculopathy; and site of (silent) stroke on imaging; and results of CBF and cerebrovascular reserve (CVR) studies. We divided presenting symptoms into four categories depending on the information provided by the authors: (1) ischemic stroke only; (2) TIA(s) only; (3) hemorrhage; or (4) other symptoms. We collected information on the level of education and occupation. In studies that provided longitudinal assessment of cognitive functioning, data were also collected for the second time-point, including the type of revascularization in surgically treated patients.

From the neuropsychological assessments we extracted the following data: mean full-scale intelligent quotient (FSIQ), developmental quotient (DQ) (pooled with FSIQ as IQ); verbal intelligent quotient (VIQ); performance intelligent quotient (PIQ); raw or standardized z-scores of cognitive tests; and the proportion of patients with cognitive impairment overall and per cognitive domain (Supplementary Table 1 summarizes the specific neuropsychological tests applied by each study). For studies that did not provide the proportion of patients with cognitive impairment, we

calculated the proportion based on published normative data if possible. For DQ (a ratio calculated by dividing the mental developmental age with the chronological age) we appointed to have the same norm sample as (FS)IQ, unless otherwise specified.[11] Cognitive test results derived from neuropsychological evaluation were grouped into six predefined cognitive domains according to standard neuropsychological practice specified in Lezak: intelligence, memory, processing speed, attention and executive functions, visual perception and construction, and language (Supplementary Table 2).[12] In studies that provided results of multiple cognitive tests investigating the same domain, we determined the mean score and, if possible, calculated the mean z-scores and standard deviations (SDs) for the domain. A z-score is a standardized score which entails the number of SDs that an individual test result differs from the mean score in healthy controls, thereby indicating the relative location of a measurement within its distribution.[13]

Data analysis

To assess the presence of cognitive impairment, we determined the median proportion of patients with cognitive impairment. Cognitive impairment was defined according to the authors' criteria, or as a cognitive score (overall, or on a specific domain, or on at least two tests) deviating more than 1.5 SD from the population mean, or IQ <85. To assess the severity of the impairment, we calculated the median cognitive scores of the various cognitive tests. To determine whether mean age, ethnicity, sex, mean duration of symptoms, and presenting symptoms were determinants of cognitive impairment, we performed linear regression analysis weighted by the inverse standard error of the proportion of patients with impaired cognition. Due to lack of data, this could not be performed for other patients' characteristics. We qualitatively determined the reported association between frontal CBF and CVR and cognitive impairment as reported by the authors.

In studies that provided longitudinal assessment of cognitive function, we determined whether cognitive functions improved, deteriorated or remained stable over time. For intelligence, we used a cut-off point of more than 10 points differences of IQ scores at follow-up. For cognitive domains, change over time was categorized according to the criteria provided by the authors.

Results

After screening 299 studies (66 studies were screened on full text), we included 17 studies reporting cognitive function in a total of 434 patients (Figure 1). Eleven studies reported on 281 children and six studies on 153 adults. Tables 1 and 2 and Supplementary Tables 3 and 4 summarize study and disease characteristics and neuropsychological test results.[4,6,9,14-27] Four studies reported on cerebral hemodynamic measures in relation to cognitive functions.[4,9,17,21] Nine studies reported longitudinal assessment of cognitive function over time, eight of which provided data after surgical treatment in children; one after conservative treatment in adults (Table 2 and Supplementary Table 5).[4,15-20,22,23] Study quality varied between three and six out of seven: three studies had a total score of 3;[4,21,22] five studies a score of 4;[16,18-20,23] five studies a score of 5;[6,9,17,25,27] and four studies a score of 6.[14,15,24,26] The most important reasons for studies having a risk of bias were: sample size <30 patients (65%) and no information on whether patients were included consecutively (87%) (Supplementary Table 6).

Children

In the 11 studies reporting on children, median age of the study cohorts was 9.4 years (range, 5.9 to 13.9); the median percentage females 55% (range, 33% to 75%; 10 studies, 268 patients). All studies except one[14] described Asian cohorts of which nine were Japanese. Two studies described the criteria they used for the diagnosis of MMV: confirmation by angio-

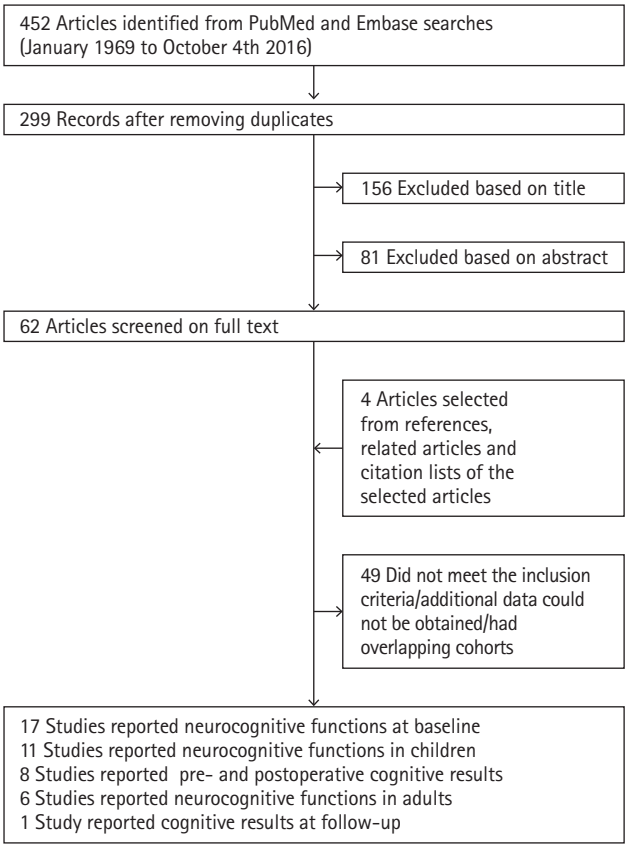

Figure 1. Flowchart.

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Table 1. Basic characteristics of studies and neuropsychological results in children and adults with moyamoya vasculopathy

Study	No.	Age (yr)	Presenting symptoms (%)	Duration (mo)	Cognitive impairment overall (%)	FSIQ impaired (%)	VIQ impaired (%)	PIQ impaired (%)	Memory impaired (%)	Procspeed impaired (%)	Att/EF impaired (%)	Visper/ const impaired (%)	Language impaired (%)
Hsu et al. (2014)[6]*	13	13.9±6.3 (6–17)†	TIA 100	17±15.9 (1–48)†	39	0	17	0	15	8	8	18	-
Williams et al. (2012)[14]*	30	10.1±4†	Infarction 50	35.0±49 (2–204)†	-	-	-	-	-	-	-	-	-
Lee et al. (2011)[15]*	65	9.1 (4–17)†	-	-	-	-	-	-	-	-	-	-	-
Imaizumi et al. (1999)[16]*	38	6.5±3.3 (1–13)†	Infarction 26 TIA 63 Other 11	16.2±16.1 (160)†	-	-	-	-	-	-	-	-	-
Ohtaki et al. (1998)[17]*	8§	7.1±2.0 (5–11)‖	Minor completed stroke 12.5 Hemorrhage 12.5 TIA 75	18.9±19.7 (2–60)‖	13	13	-	-	-	-	-	-	-
Matsushima et al. (1997)[18]*	20	9.6±3.4‖	Infarction 30 TIA 70	-	15	-	-	-	-	-	-	-	-
Matsushima et al. (1991)[19]*	50¶	9.4±4.3 (2–21)‖	Movement disorder 80 Seizures 6 Headache 10 Involuntary movements 4	55.8±50.7 (0–188)‖	50	-	-	-	-	-	-	-	-
Sato et al. (1990)[20]*	12**	5.9±2.3 (1–10)†	Ischemia 50 TIA 50%	12.6±10.6 (1–31)†	67	-	57	56	-	-	-	-	-
Tagawa et al. (1989)[21]*	10††	10.2±3.2 (6–15)†	Infarction 10 TIA 90	57.8±50.5 (13–155)†	30	30	-	-	-	-	-	-	-
Ibayashi et al. (1985)[22]*	15	9.2±3.3 (5–16)‡‡	Completed stroke 53 TIA 47	48.3±44.3 (19–136)‡‡	-	-	-	-	-	-	-	-	-
Ishii et al. (1984)[4]*	20	9.9±3.1 (5–16)‡‡	Completed stroke 60 TIA 40	-	22	22	21	26	-	-	-	-	-
Lei et al. (2017)[26]§§	26	40.2±9.4‡‡	Minor stroke 27 TIA 54 Headache 19	-	-	-	-	-	-	-	-	-	-
Kazumata et al. (2015)[27]§§	23	40.9±9.5 (21–58)‡‡	TIA 43 Asymptomatic 57	-	30	8	4	17	35	33	30	22	39
Su et al. (2013)[23]§§	26	43.7±8.6 (26–59)‡‡	Hemorrhage 100	1.2†	0	-	-	-	-	-	-	-	-
Calviere et al. (2012)[9]§§	13	36.6±12.9‡‡	Ischemic stroke 62 Hemorrhage 8 Other 30	36.1‖‖	54	-	-	-	54	23	54	23	31

Table 1. Continued

Study	No.	Age (yr)	Presenting symptoms (%)	Duration (mo)	Cognitive impairment overall (%)	FSIQ impaired (%)	VIQ impaired (%)	PIQ impaired (%)	Memory impaired (%)	Procspeed impaired (%)	Att/EF impaired (%)	Visper/ const impaired (%)	Language impaired (%)
Festa et al. (2010)[25§]	29	39.9±11.2 (20–65)[‖‖]	Ischemic stroke 72 TIA 17 Hemorrhage 3 Other 8	-	69	-	-	-	39	21[¶¶]	19***	29	20
Karzmark et al. (2008)[24§§]	36	36.6±9.9[†]	-	-	31	19	25	25	7	39	43	23	40

Values are presented as mean±standard deviation (range) or mean±standard deviation.
FSIQ, full-scale intelligent quotient; VIQ, verbal intelligence quotient; PIQ, performal intelligence quotient; Procspeed, processing speed; Att, attention; EF, executive function; Visper/const, visual perception/construction; TIA, transient ischemic attack.
*Studies reporting results in children; [†]At neuropsychological assessment; [§]At diagnosis; [§§]Excluding 2 patients (1 scaled out, 1 not investigated); [‖‖]At operation; [¶]Study included 65 patients with preoperative data in 50 patients; **Study included 13 patients from which 12 had preoperative data; [††]Study included 21 patients from which 10 had preoperative data; [‡‡]Not specified; [§§]Studies reporting results in adults; [‖‖]At presentation; [¶¶]n=19; ***n=16.

graphic evidence of moyamoya collaterals and stenosis in one study[14] and according to Sato et al.[20] in the other. One paper reported the inclusion of patients with MMS (n=20).[14] Presenting symptoms were reported in 10 studies (216 children). The median proportion of children presenting with ischemic stroke was 31% (range, 0% to 60%; nine studies, 166 patients), and with TIA only 69% (range, 40% to 100%; nine studies, 166 patients).[4,6,14,16-18,20-22] Presentation with hemorrhage was rare (one patient in 166 children in nine studies). One study (50 patients) did not report symptoms that could be classified according to our predefined categories.[19]

The median duration of symptoms was 27.0 months (range, 12.6 to 57.8). We found no information on school performance or the presence of depression among the pediatric studies.

Cognitive impairment

The median proportion of children with cognitive impairment overall was 30% (range, 13% to 67%; seven studies, 133 patients) (Figure 2) with a median IQ score of 101 (range, 71 to 107).[4,6,17-21] In the included 11 studies, the median IQ score was 98 (range, 71 to 107),[4,6,14-22] median VIQ score was 97 (range, 77 to 108; seven studies, 170 children),[4,6,14,15,18,20,22] and median PIQ score was 100 (range, 89 to 109; six studies, 163 children).[4,6,14,15,18,22] Three studies reported on specific cognitive domains.[6,14,15] Memory was affected in 15% of patients (one study, 13 patients).[6] Eight percent of the patients had impairment in processing speed and attention and executive functions, and 18% in the visual perception and construction domain (one study, 13 patients).[6] The median z-score for memory was −0.39 (range, −0.85 to 0.45; three studies, 108 children)[6,14,15] and for processing speed −0.43 (range, −0.86 to 0.00; two studies, 43 children).[6,14] One study (13 patients) assessed additional domains with mean z-scores of 0.50 for attention and executive function; and −0.53 for visual perception and construction.[6]

We found no association between mean age (B=−0.014; 95% confidence interval [CI], −0.112 to 0.083; *P*=0.723); type of presenting symptom (for infarction [B=−0.002; 95% CI, −0.017 to 0.013; *P*=0.672] and for TIA [B=−0.002; 95% CI, −0.013 to 0.017; *P*=0.672); mean duration of symptoms (B=0.000; 95% CI, −0.016 to 0.016; *P*=0.945); and proportion of females (B=−0.005; 95% CI, −0.025 to 0.014; *P*=0.508), and the proportion of patients with cognitive impairment (Supplementary Table 7).[4,6,18,20,21]

Cerebral blood flow

Three studies investigated the relation between CBF (xenon-enhanced computed tomography [CT][4] or single photon emission CT [SPECT])[17] and IQ scores.[21] In one study, patients with a lower

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Table 2. Longitudinal neuropsychological test performances

Study	FU period (mo)	Impairment overall (A/B) (%)*	Improved (%)	Stable (%)	Deteriorated (%)
Lee et al. (2011)[15†]	19[‡] (5–46)	-	-	-	-
Imaizumi et al. (1999)[16†]	>120[§]	-	-	-	-
Ohtaki et al. (1998)[17†]	85.2±32.59[‖] (23–110)	13/13	12	63	25
Matsushima et al. (1997)[18†]	113[‡]	15/20	-	-	-
Matsushima et al. (1991)[19†]	26.2±14.7[‡] (7–58)	50/49	27	49	24
Sato et al. (1990)[20†]	44.4±26.3[¶] (4–99)	67/58	PIQ 11 VIQ 29 DQ 0	PIQ 78 VIQ 57 DQ 100	PIQ 11 VIQ 14 DQ 0
Ibayashi et al. (1985)[22†]	6.5±4.9[‡] (1–17)	-	FSIQ 47 VIQ 20 PIQ 60	-	-
Ishii et al. (1984)[4†]	6–68[‡]	22/-	FSIQ 53 VIQ 13 PIQ 67	FSIQ 40 VIQ 73 PIQ 20	FSIQ 6 VIQ 13 PIQ 13
Su et al. (2013)[23**]	24[‖]	0/100	0	0	100

Values are presented as median (range), mean±standard deviation (range), or range.
FU, follow-up; PIQ, performal intelligence quotient; VIQ, verbal intelligence quotient; DQ, developmental quotient; FSIQ, full-scale intelligent quotient.
*A/B, prior neuropsychological test result/longitudinal neuropsychological test result; †Studies reporting results in children; ‡FU period defined as time of operation to NPA; §FU period defined as time from onset of disease to neurospychological assessment; ‖FU period defined as time of NPA to NPA; ¶FU period unspecified; **Studies reporting results in adults.

IQ showed a tendency for a more marked depression of mean CBF than those with a normal IQ (quantitative analysis not provided).[4] Another study reported a marked depression of CBF (qualitatively determined) in the frontal lobes in seven out of nine patients, all having normal IQ scores.[17] The third study reported no relation between abnormal patterns of CBF and IQ.[21]

Longitudinal results

Eight studies (199 patients) evaluated the effect of revascularization surgery on cognitive performances after a median follow-up period of 35.3 months (range, 6.5 to 113).[4,15-20,22] All eight studies reported IQ and one also assessed memory. Indirect revascularization was performed in 90.5% of the patients, direct in 0.5% and combined in 9%. The median proportion of children with impaired intelligence pre-operatively was 33% (range, 13% to 67%; four studies, 88 children) and at follow-up after revascularization 35% (range, 13% to 58%; four studies, 81 children).[17-20] In the other four studies proportions of children with impaired IQs were not reported post-operatively.

Median scores at follow-up were: for IQ 97 (range, 68 to 108; six studies, 161 children) with a pre-operative median IQ score in these studies of 101 (range, 71 to 107; 170 children); for VIQ 97 (range, 82 to 106; four studies, 107 children) with a pre-operative median VIQ score of 101 (range, 77 to 108; 107 children); and for PIQ 102 (range, 100 to 109; three studies, 100 children) with a pre-operative median PIQ score of 100 (range, 97 to 109; 100 children).

Based on available individual patient data, improvement in IQ (≥10 points) was observed in a median proportion of 27% of patients (range, 5.5% to 53%; five studies, 91 children),[4,17,19,20,22] no change in 56% (range, 40% to 89%; four studies, 76 children) and deterioration in 15% (range, 5.5% to 25%; four studies, 76 children). Improvement in VIQ was seen in 20% (range, 13% to 29%; three studies, 37 children),[4,20,22] no change in 65% (57% and 73%; two studies, 22 children) and deterioration in 13.5% (13% and 14%; two studies, 22 children). PIQ scores improved in 63.5% (60% and 67%; two studies, 30 patients), remained stable in 20% (one study, 15 patients) and deteriorated in 13% (one study, 15 patients).[4,22] Memory function improved after surgery (pre-operative z-score 0.45; after surgery 0.77).[15] One study in which 18 out of the 38 patients were operated on (five combined, 13 indirect) reported no improvement of IQ after revascularization (no quantitative data available).[16]

Adults

In the six studies reporting on adults, median age was 40.1 years (range, 36.6 to 43.7) and the median percentage of females 63% (range, 46% to 74%).[9,23-27] Of a total of 153 pa-

tients, 87 were Asian (57%), 56 Caucasian (37%), and 10 had another ethnicity (7%). The median proportion of adults presenting with ischemic stroke was 27% (range, 0% to 72%; five studies, 117 patients), TIA only 17% (range, 0% to 54%; five studies, 117 patients), hemorrhage 3% (range, 0% to 100%; five studies, 117 patients), and 19% (range, 0% to 57%; five studies, 117 patients) had other symptoms.[9,23,25-27] The median duration of symptoms at assessment or inclusion was 18.6 months (1.2 and 36.1 months; two studies).

Cognitive impairment

The median proportion of patients with cognitive impairment was 31% (range, 0% to 69%; five studies, 127 patients).[9,23-25,27] In the four studies investigating cognition by means of a neuropsychological test battery, the median proportion with impaired cognition on one or more of the reported domains was 42.5% (range, 30% to 69%).[9,24,25,27] The median IQ score was 95 (range, 94 to 99; three studies, 88 patients);[24,25,27] median VIQ score was 94 and median PIQ score 93 (two studies, 59 patients).

Four studies (101 patients) reported on specific cognitive domains.[9,24,25,27] The median proportion of patients with impaired memory was 37% (range, 7% to 54%), impaired processing speed 28% (range, 21% to 39%), impaired attention and executive functions 37% (range, 19% to 54%), impaired visual perception and construction 23% (range, 22% to 29%), and impaired language 35% (range, 20% to 40%).[9,24,25,27] The median z-scores (three studies, 78 patients) were: for memory −0.4 (range, −1.1 to −0.2), for processing speed −0.9 (range, −1.7 to −0.8), for attention and executive function −0.9 (range, −0.95 to −0.4), for visual perception and construction −0.4 (range, −0.5 to −0.2), and for language −0.6 (range, −0.8 to −0.15). One study of patients with an intraventricular hemorrhage (IVH) showed a mean score within the normal range (27.4±1.2 [range, 26 to 29]) on the Montreal Cognitive Assessment (MoCA).[23]

We found no association between mean age (B=−0.044; 95% CI, −0.184 to 0.096; *P*=0.387) or proportion of females (B=0.011; 95% CI, −0.031 to 0.053; *P*=0.460) and cognitive impairment (Supplementary Table 7). Analysis of the association of type of presenting symptom and cognitive impairment was not possible, because of lack of data categorized according to our predefined classification.

The mean duration of education was 12.1±3.1 years (three studies, 91 patients).[24-26] In a series of 26 patients from one study, nine finished college or a higher-level education, five primary school or less, and 12 middle school.[23] Another study of 36 patients reported that 25 participated in a full-time job,

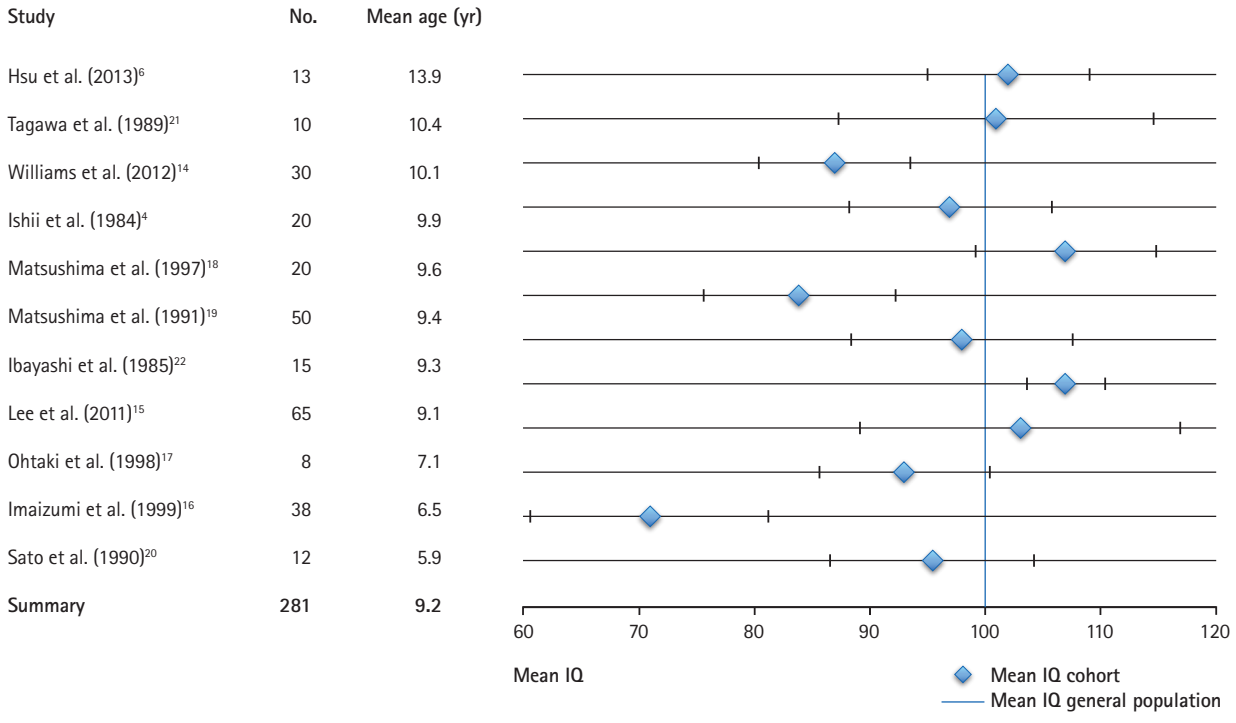

Figure 2. Mean intelligence quotient (IQ) with 95% confidence interval (CI) in children (11 studies, 281 children) ordered by mean age (mean summary IQ, 95.5; 95% CI, 86.7 to 104.2). The blue vertical line represents the mean IQ in the average population.

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five were unemployed and five were homemakers; one patient had retired.[24]

Cerebral blood flow studies

One study reported a correlation of the apparent diffusion coefficient (ADC) in normal appearing frontal white matter on diffusion weighted imaging with CVR on perfusion magnetic resonance imaging and executive functions (Spearman coefficient, –0.46; *P*=0.01).[9] Elevation of ADC was significantly correlated with executive dysfunction (area under the curve for cognitive impairment, 0.85; 95% CI, 0.59 to 1.16; *P*=0.032).

Longitudinal results

In the study assessing cognitive impairment in patients with solely IVH, all patients had normal MoCA scores at baseline (mean MoCA score 27.4±1.2 [range, 26 to 39]) and mild cognitive impairments after a mean follow-up of 24 months (mean MoCA score 18.7±1.3 [range, 16 to 21]) without treatment.[23]

Discussion

Our systematic review shows that around 30% of children and of adults have cognitive impairment. When assessed on a group level, median IQ scores are within the normal range in both children and adults. Information on specific domains of cognitive function is limited, with relatively modest impairments in memory and processing speed observed in children, and modest to large impairments across various cognitive domains in adults.

Since there was not a large discrepancy between VIQ and PIQ, total IQ scores provide a reliable insight in cognitive functioning in children. Longitudinal results in children showed that IQ scores on a group level remained within normal limits over time. In adults, longitudinal studies of neuropsychological assessments other than with a screening test have not been performed.

In a previous review, the authors concluded that cognition is affected more frequently in children than in adults, reporting intelligence to be impaired in children, and executive functions in adults.[7] However, our systematic review and meta-analysis show that in adults the proportion of patients with impairment of cognitive function is as large as in children. In comparison with this aforementioned review, we included five additional studies on children[6,14,15,21,22] and four recent studies on adults;[9,23,26,27] and excluded studies without quantitative data. Although the highest median percentage of impaired function was found in the domain attention and executive functions, we found similar proportions of patients with impairment for the other cognitive domains. In children, other domains than intelligence were investigated in only three studies. Patients with a normal intelligence may show selective cognitive impairment in other cognitive domains. Therefore, extensive neuropsychological evaluation is of great importance, also in children who generally show a diffusely impaired cognitive profile in case of cognitive deterioration because their brain is still developing.

It remains uncertain if the neurocognitive profile of patients with MMS differs from that in patients with MMD, since the presence of associated diseases was reported in only one study, which did not demonstrate a difference between these groups.[14]

We did not find an association between the predefined determinants and the proportion of patients with cognitive impairment, probably due to the limited data available. Some of the included studies suggested that age at onset[4,6,22] and longer duration of disease were[6] associated with cognitive dysfunction, however we could not confirm these associations in our meta-analysis. Previous studies were small including 13 to 20 patients and observed associations may have been due to chance. Information on the determinants of cognitive impairment and its course is scarce. The relation between cerebral perfusion and cognition in children remains unclear, whereas in adults, a single study suggested a relation between diminished perfusion in the frontal matter and executive dysfunction. Several studies have suggested that (frontal) hypoperfusion, white matter disease and infarction are associated with cognitive disturbances.[28-31] It remains unclear whether MMV directly affects cognition by chronic hypoperfusion, or that cognitive impairment is mainly the result of stroke. The observed impaired cognition in patients without stroke supports the hypothesis that chronic hypoperfusion is a contributing factor to cognitive impairment in patients with MMV.[5,6] One study reported that executive dysfunction was associated with stroke and white matter lesions and not with CVR; however, patients with higher baseline CBF had better cognitive functioning.[32] Improvement in intelligence and cerebral perfusion in children has been observed after revascularization surgery,[4,17] and for this reason frontal revascularization procedures are performed more often.[2,17,33] Whether prevention of cognitive decline should be an indication for revascularization surgery in patients with MMV remains unclear. Although our review shows that a fair number of patients improved or remained stable after revascularization, the quantity of the included data is too limited to draw final conclusions.

Although we were able to collect a reasonable amount of data on cognitive function in patients with MMV, the review was limited by the relatively low number of patients described in the individual studies. Information bias could not be avoided, given the large heterogeneity of the reported cognitive tests. Since little information on patients' characteristics was avail-

able, results could be influenced by selection bias and we could not control for confounding factors like the presence of silent infarction on imaging. Finally, we were not able to perform meta-analysis of the relation between CBF and cognition and of the effect of revascularization due to the low number and heterogeneity of studies. Our review also has strengths. We were able to quantify cognitive impairments in MMV. In addition, we were able to eliminate the risk of selection bias due to language since we did not include language restrictions. Despite these methodological shortcomings, our results give valuable insight in the presence, severity and nature of cognitive functions in MMV before and after revascularization, since we quantified cognitive impairments in MMV.

Conclusions

Large prospective studies with a standardized neuropsychological test battery are needed to determine the severity of cognitive impairment and the domains affected. Information on school level and performance, and on work status is also of importance, since it reflects function rather than deficits.[34] It remains to be established whether cognitive outcome can be improved by revascularization surgery.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2018.01550.

Disclosure

The authors have no financial conflicts of interest.

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Supplementary for Syntax

OVID Medline (PubMed) syntax

(moyamoya OR moya OR moya-moya [Title/Abstract]) AND (cognition OR neurocognitive OR intelligence OR psycho OR executive OR cognitive OR mental OR retardation OR memory OR language OR dementia [Title/Abstract])

Embase syntax

(moyamoya:ab,ti OR moya:ab,ti OR moya moya:ab,ti) AND (cognition:ab,ti OR neurocognitive:ab,ti OR intelligence:ab,ti OR psycho:ab,ti OR executive:ab,ti OR cognitive:ab,ti OR mental:ab,ti OR retardation:ab,ti OR memory:ab,ti OR language:ab,ti OR dementia:ab,ti)

Supplementary for the Risk Assessment

Newcastle–Ottawa Scale adapted[†] for cross-sectional studies

Selection: (Maximum 4 stars)

1) Representativeness of the sample[‡]
   a) Truly representative of the average in the target population*
   b) Somewhat representative of the average in the target population*
   c) No description of the derivation of the cohort

2) Sample size[§]
   a) Justified and satisfactory*
   b) Not justified

3) Selection criteria
   a) Selection criteria were clearly described and consecutive patients were included*
   b) Selection criteria were not clearly described and it was unclear whether consecutive patients were included

4) Ascertainment of the exposure[||]
   a) Validated measurement tool*
   b) Non-validated diagnostic measures (but the tool is available or described), or not all patients were DSA proven*
   c) No description of the diagnostic tool

Outcome: (Maximum 3 stars)

1) Assessment of the outcome (description of cognitive tests applied)[¶]
   a) Extensive neuropsychological evaluation**
   b) IQ*
   c) Screening test*
   d) No description

2) Quantitative data:
   a) The study reported cognitive or intellectual functioning in children and adults that allowed analysis of quantitative data.*
   b) The study did not report cognitive or intellectual functioning in children and adults that allowed analysis of quantitative data.

DSA, digital subtraction angiography; IQ, intelligence quotient.
The asterisk refers to the the number of stars (* or **) that can be assigned. It's a scoring method but not an actual footnote; [†]This scale has been adapted by the authors from the Newcastle-Ottawa Quality Assessment Scale for cohort studies[1] and the scale developed by Herzog et al. (2013)[2] to perform a quality assessment of cross-sectional studies for the systematic review: 'Cognitive functions in children and adults with moyamoya vasculopathy: a systematic review and meta-analysis.' Since there were no groups to compare (only patients with moyamoya (no control groups) were reviewed for this systematic review), we could not include the section 'Comparability'; [‡]Patients with moyamoya disease or syndrome: 1 star; [§]Sample size of n≥30: 1 star; [||] DSA or magnetic resonance angiography: 1 star; [¶]Neuropsychological test battery applied: 2 stars, IQ or screeningtest: 1 star.

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Supplementary Table 1. Applied cognitive instruments/tests for each study

Study	Applied instruments/tests*
Hsu et al. (2014)[3†]	WISC-III or WISC-IV; WAIS-III POI: Perceptual Organization Index WMI: Working Memory Index PSI: Processing Speed Index WL1: Immediate Recall of the Word List WL2: Delayed Recall of the Word List WL-recog: Recognition of the Word List CFT: Category Fluency Test JLO: Judgment of Line Orientation
Williams et al. (2012)[4†]	WISC-III or WISC-IV; WAIS-III; WPPSI-III VCI: Verbal Comprehension Index PRI: Perceptual Reasoning Index WMI PSI
Lee et al. (2011)[5†]	KEDI-WISC-R BGT recall: Bender Gestalt Test
Imaizumi et al. (1999)[6†]	WPPSI; WISC-R; WAIS-R; Tanaka-Bonet Intelligence Test Tumori-Inage Mental Development Test
Ohtaki et al. (1998)[7†]	WAIS-R; WISC-R
Matsushima et al. (1997)[8†]	WISC
Matsushima et al. (1991)[9†]	WISC; development questionnaires of Tsumori et al.
Sato et al. (1990)[10†]	WISC-R; WIPPSI; Developmental test BGT
Tagawa et al. (1989)[11†]	WISC
Ibayashi et al. (1985)[12†]	WAIS; Benton's Visual Memory Test
Ishii et al. (1984)[13†]	WISC; WAIS
Lei et al. (2017)[14‡]	TMT-B (s): Time consumed in the Trail Making Test part B MES-EX: executive subtests of Memory and Executive Screening
Kazumata et al. (2015)[15‡]	WAIS-III WSCT: Wisconsin Sorting Test TMT-A/B: Trail Making Test part A and B CPT: Continuous Performance Test Stroop test RST: Reading Span Test
Su et al. (2013)[16‡]	MoCA: Montreal Cognitive Assessment
Calviere et al. (2012)[17‡]	Letter R Category (animals) fluency test TMT-A/B Stroop interference condition Brixton test WCST-C/-P: Wisconsin Card Sorting Test number of categories and number of perseverations Colored dots and word sections of the Stroop test Verbal fluency tests Naming and Recognition Test of 80 common objects Rey figure copy test Hooper test Immediate and delayed 16 free and cued recalls Rey figure recall

Supplementary Table 1. Continued

Study	Applied instruments/tests*
Festa et al. (2010)[18‡]	WAIS-III; WASI Hopkins Verbal Learning Test California Verbal Learning Test TMT-A/B Boston Naming Test Animal Fluency COWAT: Controlled Oral Word Association Test WCST: Wisconsin Card Sorting Test Grooved Pegboard Test Hand Dynometer
Karzmark et al. (2008)[19‡]	WAIS-R; WAIS-III California Verbal Learning Test-II Memory Test-Revised Visual Reproduction subtest Delis-Kaplan Executive Function System Design Fluency Test FAS/AN: Letter and Category Fluency Tests TMT-A/B Grooved Pegboard Tactile Form Recognition Test Boston Naming Test

This table represents the cognitive instruments/tests used in each study separately.
WISC (-R or -III or -IV), Wechsler Intelligence Scale (revised or third or fourth edition); WAIS (-R or -III), Wechsler Adult Intelligence Scale (revised or third edition); WPPSI (-III), Wechsler Preschool and Primary Scale of Intelligence (third edition); KEDI-WISC-R, Korean Educational Development Institute Wechsler Intelligence Scale for Children-Revised; WASI, Wechsler Abbreviated Intelligence Scale.
*As reported by the authors; †Studies reporting results in children; ‡Studies reporting results in adults.

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Supplementary Table 2. Predefined cognitive domains according to standard neuropsychological practice specified in Lezak[20]

Cognitive domain	Included test
General intelligence	
Crystallised intelligence	Verbal IQ
	Similarities (WAIS)
	Vocabulary (WAIS)
	Information (WAIS)
	Comprehension (WAIS)
	National Adult Reading Test
	Synonyms
Fluid intelligence	Performal IQ
	Raven Progressive Matrices
	Picture Completion (WAIS)
	Picture Arrangement (WAIS)
	Arithmetic
	Category Test
Memory	
Working memory	Digit Span Forward & Backward
	Block Span Forward & Backward
	Memory Scanning Test
	Brown-Peterson task
Learning & Immediate memory	Logical Memory Immediate Recall
	Visual Reproductions Immediate Recall
	Paired Associate Learning Immediate Recall (verbal & nonverbal)
	Serial Digit Learning
	Word List Immediate Recall
	(Buschke) Selective Reminding Test Immediate Recall
	Visual Retention Test Immediate Recall
	Object Memory Immediate Recall
	Rey Complex Figure Immediate Recall
	Auditory Verbal Learning Test Immediate Recall
	Serial Learning Test
	Word/Picture Recognition Immediate Recall
	Spatial Memory Test
	California Verbal Learning Test Immediate Recall
	Claeson-Dahl Test Immediate Recall
	Seashore Tonal Memory Test
	Figural Memory Immediate Recall
	Iconic Memory
	Maze Learning Immediate Recall
	Tactual Performance Test Immediate
	Prose Recall Immediate Recall
	Symbol-Digit Learning Test
Learning & Immediate memory	Babcock paragraph Immediate Recall
	East Boston Memory Test Immediate Recall
Delayed memory	Logical Memory Delayed Recall
	Visual Reproductions Delayed Recall
	Word List Delayed Recall
	(Buschke) Selective Reminding Test Delayed Recall
	Visual Retention Test Delayed Recall
	Object Memory Delayed Recall
Cognitive domain	Included test
	Rey Complex Figure Delayed Recall
	Auditory Verbal Learning Test Delayed Recall
	Paired Associate Learning Delayed Recall (verbal & nonverbal)
	Word/Picture recognition delayed
	California Verbal Learning Test Delayed Recall
	Claeson-Dahl Test Delayed Recall
	Figural memory Delayed
	Maze Learning Delayed
	Tactual Performance Test Delayed Recall
	Delayed serial visual/verbal form memory task
	Prose Recall Delayed
	Babcock paragraph Delayed
	East Boston Memory Test Delayed Recall
	Logical Memory Delayed Recall
	Visual Reproductions Delayed Recall
	Word List Delayed Recall
	(Buschke) Selective Reminding Test Delayed Recall
	Visual Retention Test Delayed Recall
	Object Memory Delayed Recall
	Included test
	Rey Complex Figure Delayed Recall
	Auditory Verbal Learning Test Delayed Recall
	Paired Associate Learning Delayed Recall (verbal & nonverbal)
	Word/Picture recognition delayed
	California Verbal Learning Test Delayed Recall
	Claeson-Dahl Test Delayed Recall
	Figural memory Delayed
	Maze Learning Delayed
	Tactual Performance Test Delayed Recall
	Delayed serial visual/verbal form memory task
	Prose Recall Delayed
	Babcock paragraph Delayed
	East Boston Memory Test Delayed Recall

Supplementary Table 2. Continued

Cognitive domain	Included test
Processing speed	
Psychomotor efficiency	Digit Symbol Substitution
	Symbol Digit Modalities Test
	Trailmaking Test A
	Grooved Pegboard
	Purdue Pegboard
	Graded Reaction Time Task
	Perceptual Speed
Motor speed	Simple reaction time
	Fingertapping Test
	Finger Oscillation Test
Attention	
Visual attention	Stroop Color Word Test Part I & II
	Facial Recognition Test
	Target finding task
Sustained attention	Digit Vigilance Test
	Quatember & Maly's Vigilance Test
Divided attention	PASAT
Selective attention	Stroop Color Word Test Part III
Cognitive domain	Included test
Cognitive flexibility	Lexical Fluency Task
	Category Fluency Task
	Trailmaking Test B (also C, D and Color)
	Category Test
	Concept Shifting Task
	Wisconsin Card Sorting Task
	Serial subtraction (3s of 7s)
	Card Sorting
Perception & Construction	Visual Retention Test Copy
	Visual Reproductions Copy
	Block Design
	Clock Drawing
	Rey Complex Figure Copy
	Tactual Performance Test Part I
	Object Assembly (WAIS)
	Embedded Figures
	De Renzi Rods
	Flicker Fusion
	Perception of spaced stimuli
	Time judgement
	Visual Recognition Threshold
	Street Completion
	Rosen figure drawing test

Supplementary Table 2. Continued

Cognitive domain	Included test
Language	(Boston) Naming Test
	Token Test
	Boston Diagnostic Aphasia Test Writing Scale

IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale.

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Supplementary Table 3. Characteristics of studies assessing cognitive functions in children and adults with moyamoya vasculopathy

Study	Mid-year	Design	Inclusion criteria	Exclusion criteria	No.	Age (yr)	Female (%)	Ethnicity (%)	Presenting symptoms (%)	Duration (mo)	MMV site (%)	Site of stroke clinically (%)	Site of stroke imaging (%)
Hsu et al. (2014)[3]*	2010	-	Pediatric MMD >6 yr old; TIA as initial symptom	Cortical hemorrhage; prior revascularization; uncooperation; underlying systemic diseases	13	13.9±6.3 (6–17)†	-	Chinese	TIA 100	17±15.9 (1–48)†	-	-	-
Williams et al. (2012)[4]*	2004	Retro	MMD or MMS; <18 yr, NPA pre-surgery; English language skills	Whole brain radiation; severe developmental delay associated with genetic comorbidities; revascularization surgery; lack of parent/child agreement to NPA	30	10.1±4†	60	Caucasian 40 Asian 27 Black 20 Other 13	Infarction 50	35.0±49 (2–204)†	Bi 47 Uni 53	Bi 10 Uni 40	No stroke 30 Stroke 70 Bi 33 Uni 67 Cortical 57 WM 43
Lee et al. (2011)[5]*	2007	-	MMD with pre- and postoperative NPA	-	65	9.1 (4–17)†	43	Korean	-	-	Bi 82 Uni 18	-	No stroke 60 Stroke 40 MS 15 BZ 25
Imaizumi et al. (1999)[6]*	1984	-	MMD and IQ tested >once during course disease	-	38	6.5±3.3 (1–13)†	63	Japanese	Infarction 26 TIA 63 Other 11	16.2±16.1 (1–60)†	-	-	-
Ohtaki et al. (1998)[7]*	1990	Retro	Omental transplantation frontal lobes	-	8§	7.1±2.0 (5–11)‖	75	Japanese	Minor completed stroke 12.5 Hemorrhage 12.5 TIA 75	18.9±19.7 (2–60)‖	Bi 87 Uni 13	Bi 25 Uni 75	-
Matsushima et al. (1997)[8]*	-	Retro	IQ >70; EDAS performed <9.5 yr	-	20	9.6±3.4‖	40	Japanese	Infarction 30 TIA 70	-	-	-	-
Matsushima et al. (1991)[9]*	1984	-	MMD	-	50¶	9.4±4.3 (2–21)‖	56	Japanese	Movement disorder 80 Seizures 6 Headache 10 Involuntary movements 4	55.8±50.7 (0–188)‖	-	-	-
Sato et al. (1990)[10]*	-	-	Revascularization and CBF evaluation	-	12**	5.9±2.3 (1–10)†	33	Japanese	Ischemia 50 TIA 50	12.6±10.6 (1–31)†	Bi 92 Uni 8	Bi 66 Uni 33	No stroke 50 Stroke 50 Bi 50 Uni 50
Tagawa et al. (1989)[11]*	-	-	Children with MMD	-	10††	10.2±3.2 (6–15)†	60	Japanese	Infarction 10 TIA 90	57.8±50.5 (13–155)†	-	-	-
Ibayashi et al. (1985)[12]*	-	-	Juvenile MMD patients	-	15	9.2±3.3 (5–16)‡‡	53	Japanese	Completed stroke 53 TIA 47	48.3±44.3 (19–136)‡‡	-	Bi 73% Uni 27%	-
Ishii et al. (1984)[13]*	-	-	-	-	20	9.9±3.1 (5–16)‡‡	50	Japanese	Completed stroke 60 TIA 40	-	-	-	-

Supplementary Table 3. Continued

Study	Mid-year	Design	Inclusion criteria	Exclusion criteria	No.	Age (yr)	Female (%)	Ethnicity (%)	Presenting symptoms (%)	Duration (mo)	MMV site (%)	Site of stroke clinically (%)	Site of stroke imaging (%)
Lei et al. (2017)1[49§§]	2013	Pro	18–80 yr; rhanded; MMD on DSA; no abnormalities/ICH several brain locations; no surgery; physically able NPA	Significant neurological diseases; psychiatric disorders; other cerebrovasular diseases; systemic diseases; specific medication	26	40.2±9.4[††]	54	Chinese	Minor stroke 27 TIA 54 Headache 19	-	-	-	No hyperintense signals >8 mm in maximum dimension
Kazumata et al. (2015)[15§§]	2013	Pro	>20 yr; idiopathic MMD	Quasi MMD; cortical infarction/subcortical lesion >8 mm; intracranial hemorrhage; revasculari-zation surgery; neurological deficit because of stroke; comorbid illness affecting cognition	23	40.9±9.5 (21–58)[††]	74	Japanese	TIA 43 Asymptomatic 57	-	Bi 100	-	No stroke 57 Stroke 43 Bi 50 Uni 50
Su et al. (2013)[16§§]	2008	Pro	MMD with IVH; 18-60 yr; no revascularization surgery; BI >60/mRS <4; no mental disability	Other cerebrovascular diseases; AED; recurrent stroke during FU	26	43.7±8.6 (26–59)[††]	46	Chinese	Hemorhage 100	1.2[†]	-	-	IVH 100
Calviere et al. (2012)[17§§]	2002	Pro	MMD; >3 mo after stroke; no revascularization surgery	<18 yr; any associated disease potentially responsible for the arterial lesions	13	36.6±12.9[††]	64	Caucasian 86 Other 12	Ischemic stroke 62 Hemorrhage 8 Other 30	36.1[‖¶]	Bi 64 Uni 36	Bi 12 Uni 88	No stroke 29 Stroke 71 Bi 60 Uni 40 Cortical 70 SC 60 BZ 90 WM10
Festa et al. (2010)[18§§]	2002	Pro- and retro	MMD with complete NPA	(neurological) Disorders affecting cognition	29	39.9±11.2 (20–65)[‖¶]	62	Caucasian 59 Hispanic 20 Afro-american 20 Asian 21	Ischemic stroke 72 TIA 17 Hemorrhage 3 Other 8	-	Bi 86 Uni 14	-	No stroke 17 Stroke 83 Bi 75 Uni 25
Karzmark et al. (2008)[19§§]	2005	–	MMD	-	36	36.6±9.9[†]	67	Caucasian 75 Asian 17 Other 8	-	-	-	-	-

Values are presented as mean±standard deviation (range), mean±standard deviation, or mean (range). This table represents the study and patients' characteristics separated for children and adults.
MMV, moyamoya vasculopathy; MMD, moyamoya disease; TIA, transient ischemic attack; Retro, retrospective; MMS, moyamoya syndrome; NPA, neuropsychological assessment; Bi, bilateral; Uni, unilateral; WM, white matter; MS, major stroke; BZ, borderzone; IQ, intelligence quotient; EDAS, encephaloduroateriosynangiosis; CBF, cerebral blood flow; Pro, prospective; DSA, digital subtraction angiography; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; BI, Barthel Index; mRS, modified Rankin Score; AED, anti-epileptic drug; FU, follow-up; SC, subcortical; R, right.
*Studies reporting results in children; [†]At NPA; [‡]At diagnosis; [§]Excluding 2 patients (1 scaled out, 1 not investigated); [‖¶]At operation; [¶]Study included 65 patients with preoperative data in 50 patients; [**]Study included 13 patients from which 12 had preoperative data; [††]Study included 21 patients from which 10 had preoperative data; [††]Not specified; [§§]Studies reporting results in adults; [‖¶]At presentation.

Supplementary Table 4. Neuropsychological test performances

Study	Authors criteria cognitive impairment	Cognitive impairment overall (%)	Conclusion authors	Cognition screener score	% Impaired	(FS) IQ score	% Impaired	VIQ score	% Impaired	PIQ score	% Impaired	DQ score	% Impaired	Memory score	% Impaired	Procspeed score	% Impaired	Att/EF score	% Impaired	Visper/ const score	% Impaired	Language score	% Impaired
Hsu et al. (2014)[3]*	IQ: >80 normal 70–79 borderline <70 defective NPA: <1.5 SD borderline <2 SD defective	39	Normal intellectual development with specific impairments in some	-	-	102±13 (82–124)	0	99±15 (77–117)	17	103±13 (81–123)	0	-	-	(z=–0.39) 8.6±2.8	15	(z=0.00) 103.2±17.9	8	(z=0.50) 13.3±4.7	8	(z=–0.53) 21.8±4.3	18	-	-
Williams et al. (2012)[4]*	1 SD from the mean (IQ, 85–110)	-	Significant lower than test sample	-	-	87±18	-	91±14	-	89±22	-	-	-	(z=–0.85) 87.3±15.8	-	(z=–0.86) 87.2±13.2	-	-	-	-	-	-	-
Lee et al. (2011)[5]*	Compared with population averages	-	Age appropriate IQ	-	-	107±14	-	108±13	-	105±16	-	-	-	(z=0.45) 3.8±1.9	-	-	-	-	-	-	-	-	-
Imaizumi et al. (1999)[6]*	-	-	-	-	-	93±23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ohtaki et al. (1998)[7]*	IQ: >90 normal 89–70 borderline <69 retardation	13	Normal intellectual range	-	-	103±20 (58–128)	13	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Matsushima et al. (1997)[8]*	Normal IQ >86	15	-	-	-	107±18	-	105±21	–	109±13	-	-	-	-	-	-	-	-	-	-	-	-	-
Matsushima et al. (1991)[9]*	Normal IQ >86	50	-	-	-	-	-	-	-	-	-	84±30 (20–138)	50	-	-	-	-	-	-	-	-	-	-
Sato et al. (1990)[10]*	IQ: normal ≥1SD borderline –2SD to –SD: mild –3SD to –2SD moderate –3SD to –4SD	67	-	-	-	-	-	77±12[†] (58–88)	57	81±19[†] (42–104)	56	61±17[§] (42–72)	100	-	-	-	-	-	-	-	-	-	-
Tagawa et al. (1989)[11]*	-	30	Poor mental prognosis was correlated with early onset MMD	-	-	101±22 (71–134)	30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ibayashiet al. (1985)[12]*	-	-	IQ was reduced with advancing age	-	-	98±19	-	97±16	-	97±17	-	-	-	-	-	-	-	-	-	-	-	-	-
Ishii et al. (1984)[13]*	-	22	-	-	-	97±20	22	95±18	21	97±21	26	-	-	-	-	-	-	-	-	-	-	-	-
Lei et al. (2017)[14]‖	-	-	MMD patients performed worse than healthy controls	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kazumata et al. (2015)[15]‖	-	30	MMD impairs executive funtion,working memory and attention	-	-	94±13	8	95±13	4	93±11	17	-	-	-	35	-	33	-	30	-	22	-	39

Supplementary Table 4. Continued

Study	Authors criteria cognitive impairment	Cognitive impairment overall (%)	Conclusion authors	Cognition screener score	% Impaired	(FS)IQ score	% Impaired	VIQ score	% Impaired	PIQ score	% Impaired	DQ score	% Impaired	Memory score	% Impaired	Procspeed score	% Impaired	Att/EF score	% Impaired	Visper/ const score	% Impaired	Language score	% Impaired
Su et al. (2013)[16]‖	Abnormal: MoCA <25 MCI: MoCA <25≥14	0	No impairment	27.4±1.2	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Calviere et al. (2012)[17]‖	Impairment: z-score ≥1.7SD below normative mean EDS: impairment ≥3 tests	54	-	-	-	-	-	-	-	-	-	-	-	(z=–0.4)	54	(z=–1.7)	23	(z=–0.95)	54	(z=–0.5)	23	(z=–0.15)	31
Festa et al. (2010)[18]‖	Z-score ≥2 domains >1.5SD or ≥1 domain >2SD below normative mean	69	Disruption in a broad range of functions	-	-	99±17	-	-	-	-	-	-	-	z-score –1.1±1.4	39	z-score –0.8±1.1	21¶	z-score –0.4±0.8	19**	z-score –0.4±1.3	29	z-score –0.8±1.1	20
Karzmark et al. (2008)[19]‖	>50% of the scores ≥1–2SDs below the mean	31	MMD can affect cognition (mostly EF)	-	-	95±9 (z=–0.6)	19	93±8 (z=–0.5)	25	93±8 (z=–0.5)	25	-	-	(z=–0.2)	7	(z=–0.9)	39	(z=–0.9)	43	(z=–0.2)	23	(z=–0.6)	40

Values are presented as mean±standard deviation (range) or mean±standard deviation. This table is divided into overall cognitive results of the studies separated for children and adults, followed by the test results for the cognitive screener test and all the six cognitive domains.

(FS)IQ, (full-scale) intelligent quotient; VIQ, verbal intelligence quotient; PIQ, performal intelligence quotient; DQ, developmental quotient; Procspeed, processing speed; Att, attention; EF, executive function; Visper/const, visual perception/construction; IQ, intelligence quotient; NPA, neuropsychological assessment; SD, standard deviation; MMD, moyamoya disease; MoCA, Montreal Cognitive Assessment; MCI, mild cognitive impairment; EDS, executive dysfunction syndrome.

*Studies reporting results in children; †n=7; ‡n=9; §n=3; ‖Studies reporting results in adults; ¶n=19; **n=16.

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Supplementary Table 5. Longitudinal neuropsychological test performances

Study	FU period (mo)	Surgery type (n)	Impairment overall (%), A/B	Conclusion authors, A/B	% Improved	% Stable	% Deteriorated	Cognition screener score, A/B	% Impaired A/B	(FS)IQ score, A/B	% Impaired A/B	VIQ score, A/B	% Impaired A/B	PIQ score, A/B	% Impaired A/B	DQ score, A/B	% Impaired A/B	Memory score, A/B	% Impaired A/B
Lee et al. (2011)[5]*	19† (5–46)	ID 65 Bifr 42	-	Functions are maintained well before and after surgery	-	-	-	-	-	107±14/ 108±13	-	108±13/ 106±13	-	105±16/ 109±31	-	-	-	(z=0.45) 3.8±1.9/ (z=0.77) 4.5±1.7	-
Imaizumi et al. (1999)[6]*	>120†	C 5 ID 13	-	No improvement	-	-	-	-	-	93±23/-	-	-	-	-	-	-	-	-	-
Ohtaki et al. (1998)[7]*	85.2±32.59§ (23–110)	C+Bifr 8	13/13	Stable	12	63	25	-	-	103±20 (58–128)/ 96±25 (48–138)	13/13	-	-	-	-	-	-	-	-
Matsushima et al. (1997)[8]*	113†	ID 20	15/20	-	-	-	-	-	-	107±18/ 100±16	–	105±21/ 100±16	–	109±13/ 100±16	-	-	-	-	-
Matsushima et al. (1991)[9]*	26.2±14.7† (7–58)	ID 41‖	50/49	Stable	27	49	24	-	-	-	-	-	-	-	-	84±30 (20–138)/ 83±32 (35–140)	50/ 49	-	-
Sato et al. (1990)[10]*	44.4±26.3¶ (4–99)	D 1 C 1 ID 10	67/58	-	PIQ 11 VIQ 29 DQ 0	PIQ 78 VIQ 57 DQ 100	PIQ 11 VIQ 14 DQ 0	-	-	-	-	77±12 (58–88)/ 82±25 (43–112)	57/29	81±19 (42–104)/ 79±24 (41–113)	56/56	61±17 (42–72)/ 56±10 (45–62)	100/ 100	-	-
Ibayashi et al. (1985)[12]*	6.5±4.9† (1–17)	C 2 ID 13	-	Surgery is considered to be effective	FSIQ 47 VIQ 20 PIQ 60	-	-	-	-	98±19/ 99±20	-	97±16/ 94±16	-	97±17/ 102±18	-	-	-	-	-
Ishii et al. (1984)[13]*	6–68†	C 2 ID 18**	22/-	Improved	FSIQ 53 VIQ 13 PIQ 67	FSIQ 40 VIQ 73 PIQ20	FSIQ 6 VIQ 13 PIQ 13	-	-	97±20/-	-	95±18/-	-	97±21/-	-	-	-	-	-
Su et al. (2013)[16]††	24§	-	0/100	Deteriorated	0	0	100	27.4±1.2/ 18.7±1.3	0/100	-	-	-	-	-	-	-	-	-	-

Values are presented as median (range), mean±standard deviation, mean±standard deviation (range), mean±standard deviation, or range. This table is divided into overall cognitive results at follow-up of the studies separated for children and adults, followed by the test results for the cognitive screener test and the available cognitive domains.

FU, follow-up; A, prior neuropsychological test result; B, longitudinal neuropsychological test result; (FS)IQ, (full-scale) intelligent quotient; VIQ, verbal intelligence quotient; PIQ, performal intelligence quotient; DQ, developmental quotient; ID, indirect; Bifr, bifrontal; C, combined; D, direct.

*Studies reporting results in children; †FU period defined as time of operation to NPA; ‡FU period defined time from onset of disease to NPA; §FU period defined as time of NPA to NPA; ‖41 out of the 50 patients investigated postoperatively; ¶FU period unspecified; **15 out of the 20 patients investigated postoperatively; ††Studies reporting results in adults.

Supplementary Table 6. Critical appraisal of the included studies

Study	Study design	Selection				Outcome	
		Representativeness of the sample	Sample size	Selection criteria	Ascertainment of exposure	Assessment outcome	Quantitative data
Hsu et al. (2014)[3]*	Cross-sectional	+		+	+	++	+
Williams et al. (2012)[4]*	Cross-sectional	+	+	+	+	++	+
Lee et al. (2011)[5]*	Cross-sectional	+	+	+	+	++	+
Imaizumi et al. (1999)[6]*	Cross-sectional	+	+	+		+	+
Ohtaki et al. (1998)[7]*	Cross-sectional	+		+	+	+	+
Matsushima et al. (1997)[8]*	Cross-sectional	+		+	+	+	+
Matsushima et al. (1991)[9]*	Cross-sectional	+	+	+		+	+
Sato et al. (1990)[10]*	Cross-sectional	+		+	+	+	+
Tagawa et al. (1989)[11]*	Cross-sectional	+		?†	?†	+	+
Ibayashi et al. (1985)[12]*	Cross-sectional	+		?†	?†	+	+
Ishii et al. (1984)[13]*	Cross-sectional	+				+	+
Lei et al. (2017)[14]‡	Cross-sectional	+	+	+	+	+	+
Kazumata et al. (2015)[15]‡	Cross-sectional	+		+	+	++	+
Su et al. (2013)[16]‡	Cross-sectional	+		+	+	+	+
Calviere et al. (2012)[17]‡	Cross-sectional	+		+	+	++	+
Festa et al. (2010)[18]‡	Cross-sectional	+		+	+	++	+
Karzmark et al. (2008)[19]‡	Cross-sectional	+	+		+	++	+

*Studies reporting results in children; †This information could not be extracted by our translators; ‡Studies reporting results in adults.

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Supplementary Table 7. Linear regression analysis

Authors	Cognitive impairment overall (%)	Mean age	Duration symptoms (mo)	% Female	% Infarction	% TIA(s)
B (95 CI; *P*)		–0.014 (–0.112 to 0.083; 0.723)	0.000 (–0.016 to 0.016; 0.945)	–0.005 (–0.025 to 0.014; 0.508)	–0.002 (–0.017 to 0.013; 0.672)	–0.002 (–0.013 to 0.017; 0.672)
Hsu et al. (2014)[3]*	39	13.9±6.3 (6–17)	17±15.9 (1–48)	-	0	100
Ohtaki et al. (1998)[7]*	13	7.1±2.0 (5–11)	18.9±19.7 (2–60)	75	-	-
Matsushima et al. (1997)[8]*	15	9.6±3.4	–	40	30	70
Matsushima et al. (1991)[9]*	50	9.4±4.3 (1.6–21)	55.8±50.7 (0–188.4)	56	-	-
Sato et al. (1990)[10]*	67	5.9±2.3 (1–10)	12.6±10.6 (1–31)	33	31	69
Tagawa et al. (1989)[11]*	30	10.2±3.2 (6–16)	57.8±50.5 (13–155)	60	10	90
Ishii et al. (1984)[13]*	22	9.9±3.1 (5–16)	-	50	60	40
B (95 CI; *P*)		–0.044 (–0.184 to 0.096; 0.387)	-	0.011 (–0.031 to 0.053; 0.460)	-	-
Kazumata et al. (2015)[15]†	30	40.9±9.5 (21–58)	-	74	-	-
Su et al. (2013)[16]†	0	43.7±8.6 (26-59)	-	46	-	-
Calviere et al. (2012)[17]†	54	36.6±12.9	-	64	-	-
Festa et al. (2010)[18]†	69	39.9±11.2 (20–65)	-	62	-	-
Karzmark et al. (2008)[19]†	31	36.6±9.9	-	67	-	-

Values are presented as mean±standard deviation (range) or mean±standard deviation. This table represents the results of the linear regression analysis weighed by the inverse standard error of the proportion of patients with impaired cognition for the available patients' characteristics.
TIA, transient ischemic attack; CI, confidence interval.
*Studies reporting results in children; †Studies reporting results in adults.

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