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Clinical paper

Longitudinal two years evaluation of neuropsychological outcome in children after out of hospital cardiac arrest

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Abstract

Aim: To investigate longitudinal functional and neuropsychological outcomes 3–6 and 24 months after paediatric out-of-hospital cardiac arrest (OHCA). Further, to explore the association between paediatric cerebral performance category (PCPC) and intelligence.

Methods: Prospective longitudinal single center study including children (0–17 years) with OHCA, admitted to the PICU of a tertiary care hospital between 2012 and 2017. Survivors were assessed during an outpatient multidisciplinary follow-up program 3–6 and 24 months post-OHCA. Functional and neuropsychological outcomes were assessed through interviews, neurological exam, and validated neuropsychological testing.

Results: The total eligible cohort consisted of 49 paediatric OHCA survivors. The most common cause of OHCA was arrhythmia (33%). Median age at time of OHCA was 48 months, 67% were males. At 3–6 and 24 months post-OHCA, respectively 74 and 73% had a good PCPC score, defined as 1–2. Compared with normative data, OHCA children obtained worse sustained attention and processing speed scores 3–6 ($n = 26$) and 24 ($n = 27$) months post-OHCA. At 24 months, they also obtained worse intelligence, selective attention and cognitive flexibility scores. In children tested at both time-points ($n = 19$), no significant changes in neuropsychological outcomes were found over time. Intelligence scores did not correlate with PCPC.

Conclusion: Although paediatric OHCA survivors had a good PCPC score 3–6 and 24 months post-OHCA, they obtained worse scores on important neuropsychological domains such as intelligence and executive functioning (attention and cognitive flexibility). Follow-up should continue over a longer life span in order to fully understand the long-term impact of OHCA in childhood.

Keywords: Paediatric, Out of hospital cardiac arrest, Outcome, Neuropsychological assessment, Long-term

Introduction

Yearly, 9 out of 100.000 children in the Netherlands experience an Out-of-Hospital Cardiac Arrest (OHCA)[1]. In contrast to adults, non-cardiac causes are the most prevalent causes of OHCA[2–4]. The overall survival rate of OHCA children is low; approximately 90–92% die pre-hospital or during hospital admission[5,6]. In our previous observational cohort study, 56% of the children who achieved return of circulation (ROC) died after PICU admission. Death was mainly due to withdrawal of life sustaining therapies based on poor neurological prognosis (67%) or brain death (29%)[7].

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In a recent study including 1980 children with OHCA, 125 of 162 survivors (77%) had a favorable outcome at discharge expressed in a good pediatric cerebral performance category (PCPC)[6].

PCPC is often used as an outcome measure in studies describing neurological outcome after paediatric OHCA[8,9]. However, PCPC is a crude outcome on a scale ranging from 1 to 6 (normal; mild, moderate or severe disability; comatose; dead) (supplementary file 1). It is unknown whether PCPC at discharge reflects daily function at longer term and if it appropriately reflects the level of neuropsychological functioning. Neuropsychological deficits are expected as sequelae in children after cardiac arrest (CA), due to ischaemic changes in the brain during and around CA. Identification of cognitive deficits is of paramount importance as these deficits may delay or even prevent the development of academic and social skills, causing long-term restrictions in activities and participation in daily life. This phenomenon is known as growing into deficit[10].

Little is known about long-term neuropsychological functioning in OHCA survivors[11,12].

In a cross-sectional cohort of in-and-out of hospital CA survivors (median follow-up interval 5.6 years), lower scores were found for intelligence and visual memory, compared with the general population[11].

In the THAPCA trial, 85 parents of OHCA children reported, during a single interview by phone at 1-year follow-up, neurocognitive problems in their children such as problems in adaptive behaviour, communication, daily living and motor skills[12]. In this same study, most children displayed significant deficits in intelligence domains of neuropsychological tests.

Since 2012, our hospital provides a standardised multidisciplinary follow-up program for paediatric OHCA survivors with structured and repeated outpatient clinic visits including functional and neuropsychological assessments. Within this context (1) we investigated functional and neuropsychological outcomes 3–6 and 24 months after paediatric OHCA and (2) explored whether PCPC scores were associated with intellectual functioning in paediatric OHCA survivors.

Methods

Study design and participants

This prospective study was performed in children admitted to the paediatric intensive care unit (PICU) of Erasmus MC-Sophia Children's Hospital, the single tertiary-care University children's hospital providing health care to children in the southwest of The Netherlands (referral area 4 million inhabitants, 25% of the Dutch population). The Erasmus MC Ethical Review Board approved the study protocol (MEC-2019–0259). In accordance with the Dutch law, signed informed consent was not required at moment of inclusion.

We included children (0–17 years) who experienced OHCA between 2012 and 2017 and survived to hospital discharge. OHCA was defined as unresponsiveness with absent palpable pulse, no signs of life, or healthcare provider perceived need for chest compressions for at least one minute[7].

Exclusion criteria were a pre-arrest PCPC score >3 and children diagnosed with a neurodegenerative disease.

Data collection

As part of standard care children were invited to our multidisciplinary follow-up program at the outpatient clinic 3–6 and 24 months post-OHCA. Functional outcomes were assessed by an experienced paediatric neurologist (MH) and paediatric intensivist (CB) through a semi-structured interview with children and their parents/-caregivers and through physical and neurological exams. When no follow-up visit took place, these outcomes, if available, were collected from notes in the patient records (records of hospital visits with other physicians). Neuropsychological outcomes were assessed by an experienced psychologist. If neuropsychological testing was performed elsewhere, results were retrieved after parental consent.

Demographical and OHCA variables

The following variables were retrospectively collected from ambulance registration forms and in hospital electronic health records: 1. Baseline patient characteristics (e.g. gender, age, socioeconomic status (SES) parents, pre-arrest PCPC), 2. OHCA and post-OHCA characteristics (aetiology, first monitored rhythm, bystander cardiopulmonary resuscitation (CPR), duration CPR, first pH and lactate), and 3. Medical outcome (survival and PCPC at hospital discharge). The SES was calculated using a 'Status Score' divided into tertiles to interpret a 'low status', middle status' and 'high status'[13]. The 'Status Score' is based on income, education level and unemployment rate by postal code.

Outcomes measures

Functional outcomes

The following functional outcomes were assessed: PCPC score, school attendance, motor deficits and epilepsy. PCPC scores were dichotomised into 'good' outcome (score 1 and 2) or 'poor' outcome (scores 3–6)[6].All PCPC scores were determined by a paediatric neurologist (MH).

Neuropsychological outcomes

Validated, age-appropriate neuropsychological tests and questionnaires with Dutch normative testdata were used to assess a broad range of neuropsychological domains, see supplementary file 2 for detailed description.

1. Development and intelligence in children (all ages): age-appropriate versions of the Bayley Scales of Infant Development or the Wechsler Scales (BSID-II, Bayley-III, WPPSI-III, WISC-III or WAIS-IV)[14–17].
2. Selective attention: Stroop Color Word Test (≥8 years)[18].
3. Sustained attention: Bourdon-Vos cancellation test (≥6 years)[19].
4. Processing speed: from the Wechsler Scales (WPPSI-III, WISC-III or WAIS-IV) (≥4 years) [14–16].
5. Visual motor integration: Beery Developmental Test of Visual Motor Integration (Beery-VMI) (≥2 years)[20].
6. Verbal memory: Rey auditory verbal learning test (Rey-AVLT), delayed recall (≥6 years)[21,22].
7. Visual memory: Rey-Osterrieth complex figure test (Rey-CFT) recognition (≥6 years)[23].

8. Executive functions (cognitive flexibility): Trail-Making Test part B (TMTB) (≥8 years)[24].
9. Parent-reported executive function: Behaviour Rating Inventory of Executive Function questionnaires (BRIEF-P or BRIEF) (≥2 years)[25].

Statistical analyses

Outcomes of participants and non-participants were compared with independent sample t-tests for normally distributed continuous data, Mann–Whitney U tests for non-normally continuous data and Fisher's exact test for dichotomous data. Normality of all data was examined with the Shapiro-Wilk test.

Neuropsychological outcome standard scores were converted into Z-scores by calculating the difference with the test-mean, divided by the test-SD. A negative Z-score reflects a worse score compared with the norm (for comparable interpretation, BRIEF z-scores were multiplied by −1). One-sample t-tests were performed to compare neuropsychological outcomes of OHCA survivors with the normative Z-score = 0.

Repeated measures of participants at 3–6 and 24 months were compared with non-parametric paired tests (Wilcoxon signed rank tests) for continuous Z-scores. Due to the explorative design of this study, no correcting for multiple testing was performed. Correlations between PCPC and intellectual functioning were analyzed using Kendall's tau-b.

All analyses were performed with SPSS 25.0 for Windows. Results were considered statistically significant at p values <0.05.

Results

Between January 2012 and December 2017, 113 children were admitted to the PICU following ROC post-OHCA (Fig. 1). Of these 113 children, 51 (45%) survived to hospital discharge. Two were excluded due to pre-arrest PCPC > 3.

In the eligible sample of 49 children, the most common causes of OHCA were (33%) arrhythmia and near-drowning (31%) (supplementary file 3). At time of OHCA, median age was 48 months (IQR 17–166) and 67% were males. SES was low in 20%, middle in 61% and high in 16%, which was significantly lower than the SES distribution in the Netherlands[26]. Median PCPC score at hospital discharge was 2 [IQR 1–3], with good outcome in 73%.

Demographical and OHCA variables between neuropsychological tested and non-tested children were overall comparable (supplementary file 4). Except that tested OHCA children were significantly older than non-tested children at 3–6 months (p = 0.03).

Outcome 3–6 months after OHCA

Of the eligible 49 children, 36 (73%) visited the outpatient clinic. Twenty-six (53%) children underwent neuropsychological assessment. Reasons for no follow-up visits and testing are described in Fig. 1. One child with severe neurological sequelae died 6 months post-OHCA due to pneumonia. One child could not be tested neuropsychologically due to severe neurological deficits post-OHCA.

Functional outcomes

Of the 49 children, 20/24 school-aged children (83%) returned to school. One patient attending secondary education changed to a lower education level due to cognitive problems related to OHCA. One child was diagnosed with epilepsy. Neurological exam revealed hemiparesis in 5 and tetraparesis in 2 children (14%) (Gross Motor Function Classification System (GMFCS) varying from I-V[27]). Median PCPC score was 2 [IQR 1–3]; 36 children (74%) had a good outcome (Table 1).

Neuropsychological outcomes

In the 26 children who underwent neuropsychological assessment, verbal, performance, and total IQ scores did not differ significantly from norm data (Table 2). Significantly lower scores, compared with norm data, were found for sustained attention and processing speed; respectively 88% and 47% of the children scored >1 SD below the norm (in the general population 16% is expected), see Table 2. Median Z-scores for most neuropsychological domains were lower than zero, Fig. 2.

Outcome 24 months after OHCA

Of 48 eligible children (one patient died 6 months post-OHCA), 27 children (56%) visited the outpatient clinic and 27 (56%) underwent neuropsychological assessment. One child who visited the outpatient clinic could not be tested due to severe neurological deficits post-OHCA, Fig. 1.

Functional outcomes

Of these 48 children, 26/32 school-aged children (81%) went back to school. Due to cognitive problems related to OHCA, 2 children at regular primary school changed to a different school with smaller groups and 2 secondary school children changed to a lower education level. Neurological exam revealed hemiparesis in 4 children, tetraparesis in 1 child and 1 child had ataxia (15%) (GMFCS varying from I-V (27)) (Table 1). Median PCPC score was 2 [IQR 1–3.5]; 35 children (73%) had good outcome.

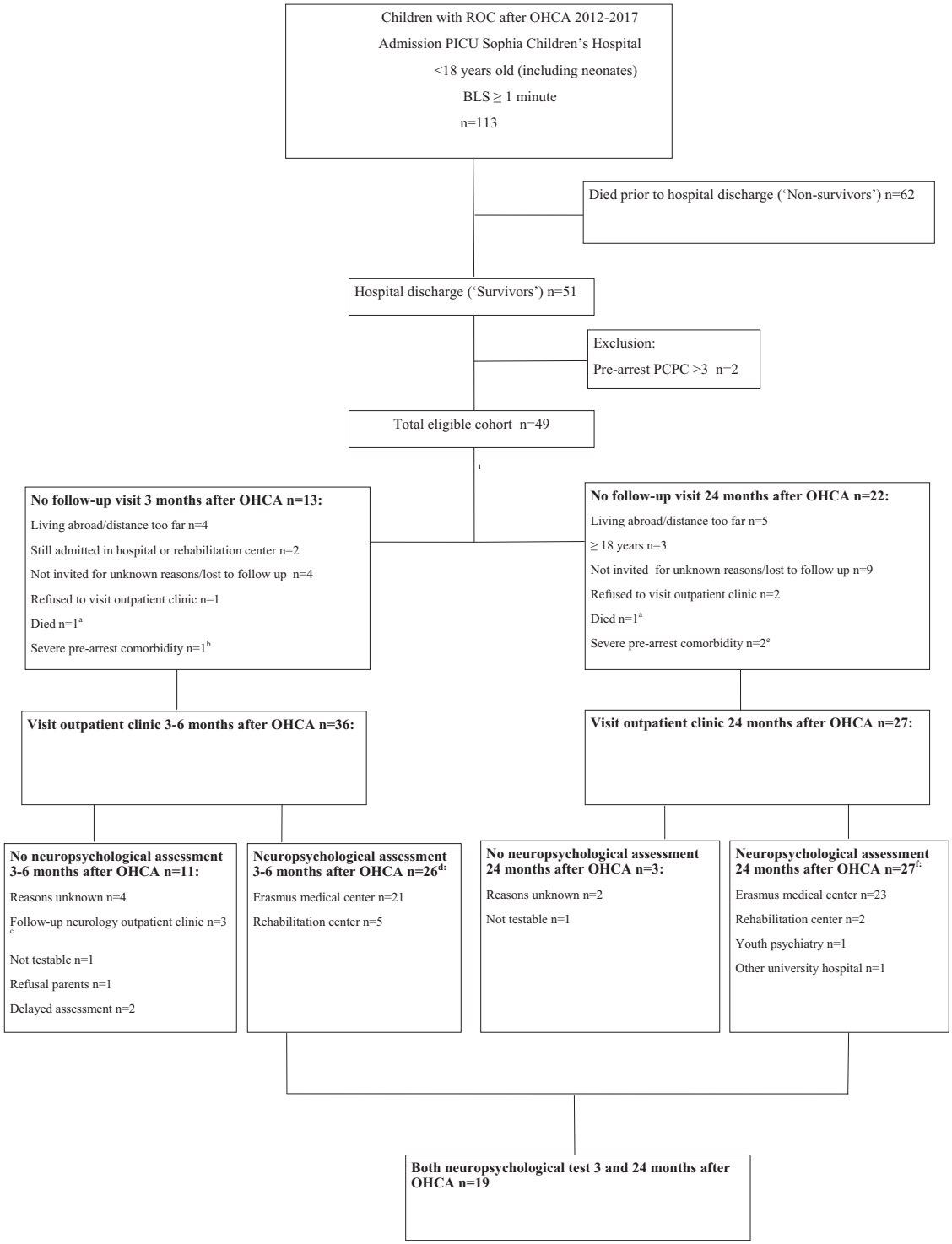
Neuropsychological outcomes

In the 27 children with neuropsychological assessment, total, verbal, and performance IQ scores were lower compared with normative data; respectively 46%, 46%, and 38% of the children scored >1 SD (15 IQ points) below the mean norm score (Table 2). They also obtained worse scores for selective attention, sustained attention, processing speed, and cognitive flexibility compared with norm data; respectively 70%, 83%, 58% and 60% scored >1 SD lower than the norm (Table 2). Median Z-scores for most domains were lower than zero, Fig. 2.

Repeated measures 3–6 and 24 months

In 38 of 49 patients, PCPC scores were assessed at both 3–6 and 24 months: in 32 (85%) PCPC remained good (1–2), in 4 (10%) remained poor (PCPC > 2), and in 2 children (5%) PCPC improved from poor to good.

In 19 patients (39%) with repeated neuropsychological testing, total, verbal and performance IQ scores and neuropsychological domain scores did not change significantly (supplementary file 5 and 6, Fig. 3).



[a] Severe neurological sequelae, PCPC at hospital discharge 5, died 3 months post-OHCA due to a pneumonia in a pediatric nursing home

[b] Hematological malignancy

[c] At neurology outpatient clinic neuropsychological assessment is not standard care

[d] 1 patient didn't visit the follow-up outpatient clinic, but neuropsychological assessment was performed in rehabilitation center.

[e] One patient hematological malignancy and one patient genetic disorder (at 3-6 months nog diagnosed yet)

[f] 3 patients didn't visit the follow-up outpatient clinic, but neuropsychological assessment was performed in another university hospital or by a different department in Erasmus Medical Center

BLS= basic life support; ROC= return of circulation; OHCA= out of hospital cardiac arrest; PCPC= pediatric cerebral performance category; PICU= pediatric intensive care unit

Table 1 – Characteristics and functional outcome of OHCA survivors and participants neuropsychological assessment 3–6 and 24 months after OHCA.

	All patients *n* = 49	Tested 3–6 months *n* = 26	Tested 24 months *n* = 27	
Characteristics				
Age at admission (months)	48 (17–166)	90 (31–177)	88 (32–164)	
Gender male	33 (67)	19 (73)	18 (67)	
Bystander CPR	39 (80)	22 (85)	22 (73)	
Initial rythm shockable	17/34 (50)	12/19 (63)	12/21 (57)	
Duration CPR (min)	10 (3–20)	10 (3.5–20)	8 (3–44)	
Missing, *n*	10	5	6	
First lactate	6.3 (4.5–12.8)	6.0 (4.5–13.4)	5.6 (4.4–13.3)	
Missing, *n*	3	1	3	
First pH	7.1 (7.0–7.3)	7.2 (7.0–7.3)	7.2 (7.1–7.3)	
Missing, *n*	4	1	4	
Etiology arrest				
Cardiac	20 (41)	12 (46)	10 (37)	
Respiratory	21 (43)	11 (42)	13 (48)	
Other	8 (16)	3 (12)	4 (15)	
PCPC discharge	2 (1–3)	2 (1–2)	2 (1–3)	
SES				
Low	10 (20)	6 (23)	8 (30)	
Middle	30 (61)	16 (62)	17 (63)	
High	8 (16)	4 (15)	2 (7)	
Functional outcome	**All patients at 3–6 months** ***n* = 49**	**Tested patients at 3–6 months** ***n* = 26**	**All patients at 24 months** ***n* = 48**[a]	**Tested patients at 24 months** ***n* = 27**
PCPC				
Poor	7 (14)	2 (8)	3 (6)	2 (8)
Good	36 (74)	24 (92)	35 (73)	24 (92)
Missing, n	6 (12)	0	10 (21)	0
Return to school[b]	20 (83)	14 (88)	26 (81)	22 (96)
Missing, *n*	2 (10)	0	5 (16)	1
Epilepsy	1 (2)	0 (4)	0	0
Missing, *n*	8	0	16	2
Neurological motor deficits[c]	7 (14)	5 (19)	6 (13)	4 (15)
Missing, *n*	9	0	11	1

Data are presented as *n* (%) or median (IQR: 25th−75th percentile).

CPR = cardiopulmonary resuscitation, PCPC = pediatric cerebral performance category scale, SES = socioeconomic status.

[a] *N* = 48, 1 patient died at 6 months.

[b] Only applicable for children beyond the age of 4. At 3–6 months $N \geq 4$ yrs = 24, at 24 months $N \geq 4$ yrs = 32.

[c] Motor symptoms: hemiparesis, tetraparesis or ataxia (Gross Motor Function Classification System (GMFCS) varying from I-V).

Fig. 1 – Flowchart of included patients, see attachment, [a]Severe neurological sequelae, PCPC at hospital discharge 5, died 6 months post-OHCA due to a pneumonia in a paediatric nursing home, [b]Hematological malignancy, [c]At neurology outpatient clinic neuropsychological assessment is not standard care, [d]1 patient didn't visit the follow-up outpatient clinic, but neuropsychological assessment was performed in rehabilitation center, [e]One patient hematological malignancy and one patient genetic disorder (at 3–6 months nog diagnosed yet), [f]3 patients didn't visit the follow-up outpatient clinic, but neuropsychological assessment was performed in another university hospital or by a different department in Erasmus Medical Center, BLS = basic life support; ROC = return of circulation; OHCA = out of hospital cardiac arrest; PCPC = paediatric cerebral performance category; PICU = paediatric intensive care unit.

Table 2 – Z-scores neuropsychological outcome 3 and 24 months after OHCA.

Neuropsychological outcome[a]	3–6 months				24 months			
	n[b]	*Z-score Median*	*p vs norm*	*n (%) z ≤ −1*[c]	*n*[b]	*Z-score Median*	*p vs norm*	*n (%) z ≤ −1*[c]
Total IQ (all)	21	−0.3 (−1.0 to 0.4)	0.13	6 (29%)	24	−0.4 (−1.5 to 0.2)	0.008	11 (46%)
Verbal IQ (all)	16	−0.1 (−1.1 to 0.3)	0.28	4 (25%)	13	−0.5 (−1.6 to 0.4)	0.05	6 (46%)
Performance IQ (all)	17	−0.5 (−1.3 to 0.3)	0.07	6 (35%)	13	−0.5 (−2.0 to 0.0)	0.02	5 (38%)
Selective attention (STROOP ≥ 11y)	8	0.1 (−0.1 to 0.4)	0.59	2 (25%)	10	−1.3 (−1.6 to −0.5)	0.02	7 (70%)
Sustained attention (Bourdon SD ≥ 6y)	8	−2.9 (−4.8 to −1.4)	0.01	7 (88%)	12	−4.7 (−7.4 to −2.2)	0.002	10 (83%)
Processing Speed (≥4y)	15	−0.8 (−1.3 to 0.1)	0.01	7 (47%)	19	−1.00 (−1.8 to 0.0)	0.003	11 (58%)
VMI (Beery ≥ 2y)	12	0.0 (−1.1 to 0.3)	0.20	3 (25%)	17	−0.7 (−1.1 to 0.2)	0.08	6 (35%)
Verbal Memory (Rey-AVLT, delayed recall ≥ 6y)	10	−0.6 (−2.3 to 0.8)	0.33	5 (10%)	13	0.2 (−1.1 to 1.1)	0.82	4 (31%)
Visual Memory (ReyRecog ≥ 5y)	9	−1.1 (−2.3 to 0.5)	0.15	5 (56%)	12	−0.4 (−0.8 to 0.2)	0.28	2 (17%)
Cognitive flexibility (TMTB ≥ 8y)	9	−0.7 (−2.0 to 0.2)	0.13	4 (44%)	10	−1.2 (−2.0 to −0.1)	0.04	6 (60%)
BRIEF Total score (≥2y)	9	0.0 (−1.5 to 1.8)	0.86	2 (22%)	19	0.0 (−1.0 to 0.4)	0.41	5 (26%)

[a] All neuropsychological tests were converted into Z-scores and compared with norm testdata. A higher Z-score means a better outcome.
[b] Numbers of patients differ for neuropsychological tests due to different age ranges and diversity of tests when children were tested elsewhere.
[c] Expected % in general population with Z-score ≤−1 = 16%

Correlation PCPC and intellectual functioning

No correlations were found between PCPC scores and total, verbal, or performance IQ scores on both moments: at 3–6 months, *r* ranged from −0.10 to 0.08; at 24 months, *r* ranged from −0.15 to −0.05, data not shown.

Discussion

To our knowledge, this is the first prospective, longitudinal study on neuropsychological outcomes in paediatric OHCA survivors over a 24 months period.

Among survivors, 3–6 and 24 months post-OHCA respectively 74% and 73% had good outcome expressed in PCPC, defined as score 1–2. Only a minority had motor deficits on neurological exam.

The majority of school-aged children (81%) went back to school without change in school level after 24 months.

Worse scores were found on sustained attention and processing speed compared with norm data at both time-points. Additionally, at 24 months, worse scores were also found on intellectual functioning, selective attention, and cognitive flexibility compared with norm data. In children who underwent neuropsychological testing at both time points no significant changes in neuropsychological outcomes were

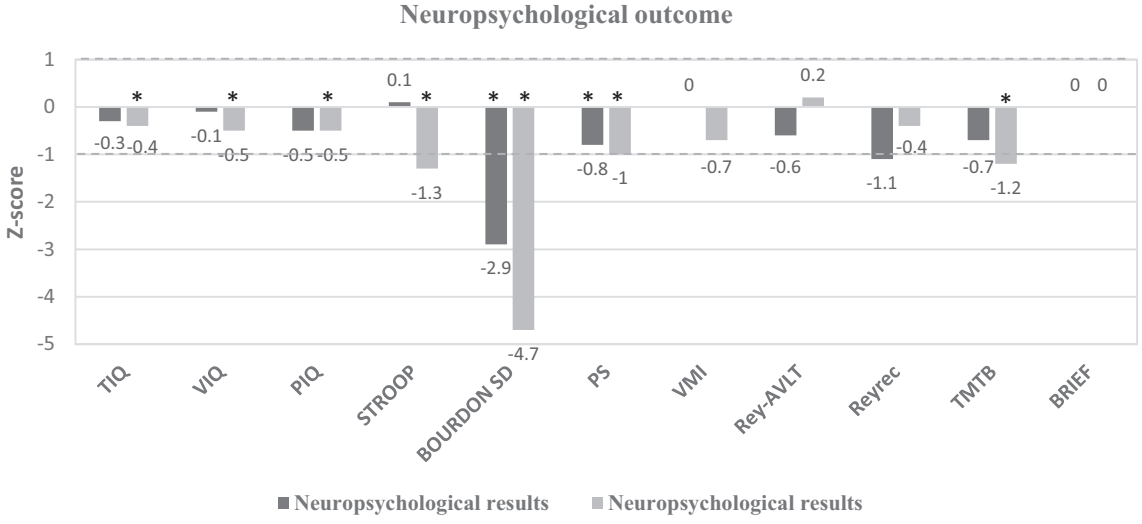


Fig. 2 – Neuropsychological outcome at 3–6 and 24 months, median Z-score per domain, *Median score significantly lower compared to norm testdata., All neuropsychological tests were converted into Z-scores. A higher Z-score means a better outcome., BRIEF = Behaviour Rating Inventory of Executive Function questionnaires; Bourdon = Bourdon Vos cancellation test; PIQ = performance intelligence quotient; PS = processing speed; Stroop = Stroop Color Word Test; Rey-AVLT = Rey auditory verbal learning test; Reyrec = Rey-Osterrieth complex figure test Color Word Test; TIQ = total intelligence quotient; TMTB = Trail-Making Test part B; VIQ = verbal intelligence quotient; VMI = Beery Developmental Test of Visual Motor Integration.

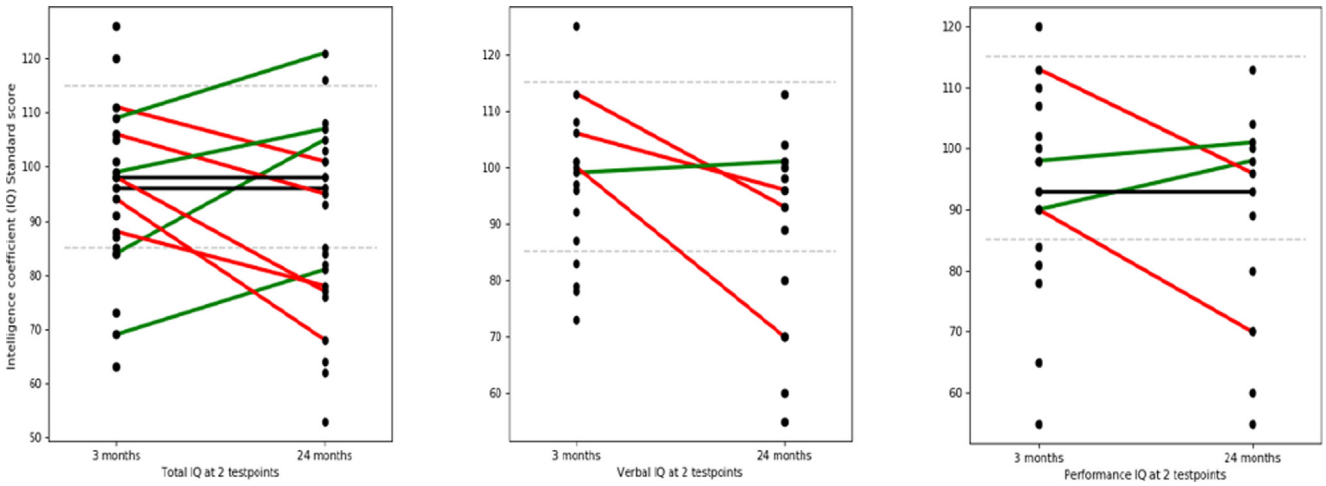


Fig. 3 – Intelligence tests and its individual course over time. Every dot represents an individual patient. Connected line means repeated measurements for an individual patient, green: improvement over time, red: decline over time, black: no difference over time. Area between the horizontal dotted lines represents the age-appropriate scores (−1SD to +SD). Standard score: higher is better functioning (mean norm 100, SD15).

found over time. Intelligence scores of OHCA children did not correlate with their PCPC scores.

Functional outcomes

The finding that only a minority (around 15%) of our survivors showed motor deficits at neurological exam 3–6 and 24 months post-OHCA seems in contrast with the findings of the THAPCA trial that reported neurological impairments in 55% of children 1 year post-arrest[28]. However, in the THAPCA trial these impairments were not only based on motor function but also on language production and comprehension, cognition and behaviour, making comparison with only motor deficits in our cohort difficult.

In our cohort, PCPC scores at hospital discharge (73% 1–2) were in line with those reported by previous research[1,6,12]. Silverstein et al. showed that PCPC scores of paediatric OHCA survivors at hospital discharge significantly correlated with PCPC at 3 and 12 months[29]. Our findings at 3–6 and 24 months suggest the same since the percentage of patients with good outcome at discharge remained unchanged over time.

Neuropsychological outcomes

At 3–6 months a selection bias may have occurred because of a trend (p = 0.07) towards more favourable PCPC scores in the neuropsychologically tested group compared with the non-tested group. Therefore the finding that OHCA children scored worse on sustained attention and processing speed and not on other outcomes at this time-point should be interpreted with caution.

At 24 months follow-up, OHCA children obtained worse intelligence scores compared to norms, which is consistent with outcomes of other paediatric post-CA studies[11,12,30]. Additionally, worse scores for attention, cognitive flexibility, and processing speed were detected. This was also found in the THAPCA trial in which both IHCA and OHCA survivors were tested one year after CA[30].This is remarkable, since there are differences between the present study and the THAPCA study. The THAPCA trial 1). Included IHCA and OHCA children when they were unresponsive and mechanically ventilated after ROC, creating a population with possibly more severely affected children, 2). Included a fraction of eligible children presenting to the hospital (295/1355, 22%), 3). Had a different study design comparing the efficacy of therapeutic hypothermia with therapeutic normothermia, 4). Had a smaller inclusion period; 2009-2012 in THAPCA versus 2012-2017 in present study, and 5). The follow-up included a cross-sectional assessment moment at 1 year follow-up versus longitudinal follow-up over 2 years in the present study.

Lower intelligence scores were also found at 2 years follow-up in a large heterogeneous cohort of critically ill PICU survivors (n = 786), implicating that critical illness itself has negative impact on intelligence[31].

In those children who were assessed repeatedly, no significant changes were found in intelligence scores and neuropsychological outcomes over time. Unfortunately, the sample with repeated measures was small (median n = 5 per domain) with a wide age range. This makes it difficult to draw definite conclusions.

Intelligence scores of OHCA children did not correlate with PCPC scores. Silverstein et al. found that PCPC scores were correlated with scores on the Vineland Adaptive Behavior Scales (VABS)[29]. However, their inclusion criteria and assessment method (parent-reported versus objectively tested intellectual functioning) differed from our study, and it is not possible to compare the score of the VABS with tested intellectual functioning.

In conclusion, although the gross outcome during follow-up was favourable in our OHCA children, they do have cognitive deficits, making them cognitively vulnerable during development. What does this mean for the future of these children? Due to several factors, this is difficult to predict from our study: the median age in our cohort was 48 months at arrest, with a wide age range of 3 months up to 18 years. Besides, the longer-term impact and development of these cognitive vulnerabilities throughout their academic career and participation in daily life are still unclear. From follow-up studies in other children with vulnerable brains (e.g. with acquired brain injury after trauma or brain tumor treatment) we know that these children may grow into deficit over time[32–35].

Strengths and limitations

Strength of our study is our representative study-population. Characteristics such as age, OHCA cause and distribution of sex are comparable with previous research[2,6]. Furthermore, our cohort was homogeneous including solely OHCA survivors with a normal functioning pre-arrest with on-site visits at our outpatient clinic at standardised moments, including repeated neuropsychological testing up to 24 months after the OHCA event. Besides general intelligence scores, other more complex neuropsychological domains were assessed using validated, age-appropriate tests.

As to limitations, the relatively high percentage of good PCPC scores may reflect a selection bias due to the high amount of withdrawal of intensive care treatment of children with an expected poor neurological outcome[7].

Our cohort was small ($n = 49$) with a wide age-range. Due to age limitations, most neuropsychological domains were only tested in older children. When children were tested repeatedly, test batteries were not always the same. In our patients SES was significantly lower than the general Dutch population, which might have influenced the neurocognitive outcome.

When we started the follow-up program, initially the loss to follow-up was high. This improved over time due to a more structured program. Due to these limitations, we were not able to find predictors for neurocognitive outcomes. We also did not include brain imaging as part of our standardised follow-up. Finally, in general OHCA children are offered structured rehabilitation or paramedical programs after discharge. When we started our follow-up program we initially didn't inquire about this routinely. This resulted in many missing data, therefore we did not include this aspect in our description of the study population.

Future directions

Our findings underline the need for a standardised follow-up program (internationally) into adulthood as standard of care in OHCA survivors. In our opinion, this follow-up should include neurological and neuropsychological assessments; it should provide care by an educational psychologist to monitor these children during their development into adulthood and to provide parents a realistic view of the strengths and weakness in their child's intellectual functioning. Neuropsychological assessment should include intelligence scores, attention, processing speed, memory and executive functioning. Moreover, psychosocial functioning, quality of life and participation, may add useful information regarding functioning of OHCA children in daily life.Furthermore, to improve outcome, it is important to provide OHCA children and their families with resources and education after critical illness and PICU admission[36] .In 2021, a pediatric core outcome set for CA in children (P-COSCA) has been developed, with the purpose to avoid inconsistencies in research regarding outcome after pediatric CA[37]. A core set of 5 outcomes was identified; survival, brain function, cognitive function, physical function, and basic daily life skills at different time points post-CA. Additionally, a scientific statement has been published recently describing many outcome domains after sudden CA, not only for the individuals themselves, but also for their care providers and community[38]. We recommend that future research on outcome after CA should adhere to these scientific statements.

To answer the" growing into deficit" question, larger cohorts should be assessed into adulthood. One possible way to achieve this is to establish a long-term follow-up program within multicenter international collaborations like the Pediatric Resuscitation Quality Collaborative (PediRES-Q)[39].

Conclusions

Outcome expressed in PCPC was good in the majority of paediatric OHCA survivors at 3–6 months and 24 months post-OHCA. Neuropsychological assessment showed adverse outcome at 3–6 and 24 months, in domains of attention and intelligence, although most children returned to their original school. PCPC scores were not associated with intelligence scores. Due to the relatively young age of our cohort, follow-up should continue over a longer life span in order to fully understand the long-term consequences and impact of OHCA in childhood.

CRediT authorship contribution statement

Hunfeld: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Dulfer:** Data curation, Methodology, Formal analysis, Supervision, Writing review & editing. **Rietman:** Writing review & editing, Supervision, Methodology. **Pangalila:** Writing review & editing. **van Gils-Frijters:** Data curation, Writing review & editing. **Catsman:** Conceptualization, Supervision, Writing review & editing. **Tibboel:** Conceptualization, Supervision, Writing review & editing. **Buysse:** Conceptualization, Supervision, Methodology, Writing review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.07.043.

REFERENCES

1. Bardai A, Berdowski J, van der Werf C, et al. Incidence, causes, and outcomes of out-of-hospital cardiac arrest in children a comprehensive, prospective, population-based study in the Netherlands. J Am Coll Cardiol 2011;57(18):1822–8.
2. Moler FW, Donaldson AE, Meert K, et al. Multicenter cohort study of out-of-hospital pediatric cardiac arrest. Crit Care Med 2011;39 (1):141–9.

3. Topjian AA, Berg RA. Pediatric out-of-hospital cardiac arrest. Circulation 2012;125(19):2374–8.
4. Kitamura T, Iwami T, Kawamura T, et al. Conventional and chest-compression-only cardiopulmonary resuscitation by bystanders for children who have out-of-hospital cardiac arrests: a prospective, nationwide, population-based cohort study. Lancet 2010;375 (9723):1347–54.
5. Fink EL, Prince DK, Kaltman JR, et al. Unchanged pediatric out-of-hospital cardiac arrest incidence and survival rates with regional variation in North America. Resuscitation 2016;107:121–8.
6. Jayaram N, McNally B, Tang F, Chan PS. Survival after out-of-hospital cardiac arrest in children. J Am Heart Assoc 2015;4(10). https://doi.org/10.1161/JAHA.115.002122.
7. Hunfeld M, Nadkarni VM, Topjian A, et al. Timing and cause of death in children following return of circulation after out-of-hospital cardiac arrest: A single-center retrospective cohort study. Pediatr Crit Care Med 2021;22:101–13.
8. Geocadin RG, Callaway CW, Fink EL, et al. Standards for studies of neurological prognostication in comatose survivors of cardiac arrest: A scientific statement from the American Heart Association. Circulation 2019;140:e517–42.
9. Fiser DH. Assessing the outcome of pediatric intensive-care. J Pediatr 1992;121(1):68–74.
10. Rourke BP, Fisk JL, et al. Child neuropsychology. An introduction to theory, research, and clinical practice. New York, NY: The Guilford Press; 1983.
11. van Zellem L, Buysse C, Madderom M, et al. Long-term neuropsychological outcomes in children and adolescents after cardiac arrest. Intensive Care Med 2015;41(6):1057–66.
12. Slomine BS, Silverstein FS, Christensen JR, et al. Neurobehavioral outcomes in children after out-of-hospital cardiac arrest. Pediatrics 2016;137(4):e20153412. https://doi.org/10.1542/peds.2015-3412.
13. Statistics Netherlands; 2019. Available from: https://www.cbs.nl/en-gb.
14. Hendriksen JHP. WPPSI-III NL. Wechsler Preschool and Primary Scale of Intelligence. Nederlandstalige bewerking. Afname- en scoringshandleiding. [Dutch version of the WPPSI-III]. Third Edition ed. Pearson, Amsterdam; 2009.
15. Kort W, Schittekatte M, Dekker PH, Verhaeghe P, Compaan EL, Bosmans M, Vermeir G. WISC-III NL Wechsler Intelligence Scale for Children. Handleiding en Verantwoording [Dutch version of the WISC-III]. 3rd ed. Amsterdam: Harcourt Test Publishers/Nederlands Instituut voor Psychologen; 2005.
16. Wechsler D. Wechsler adult intelligence scale. Nederlandstalige bewerking. [Dutch version of the WAIS-IV]. 4th ed. Amsterdam: Pearson; 2012.
17. Smrkovsky M. Bayley Scales of Infant Development II - Nederlandse versie (BSID-II-NL). 2nd ed. Swets Test Publishers; 2002.
18. Schmand B, Houx P, de Koning I. Normen voor Stroop Kleurwoord Tests, Trail Making Test en Story Recall van de Rivermead Behavioral Memory Test [Dutch reference data for the Stroop, TMT]: Sectie Neuropsychologie. Amsterdam: Nederlands Centrum voor Psychologen; 2005.
19. Vos P. Bourdon Vos Test. Nederlandse editie: Pearson, Amsterdam; 1998.
20. Beery KE, Beery NA. The Beery-Buktenica developmental test of visual-motor integration. 5th ed. Minneapolis: Pearson; 2004.
21. Schmand B, Houx P, de Koning I. Normen. 15-Woordentest [Dutch reference data for the RAVLT]. sectie Neuropsychologie, Nederlands Instituut van Psychologen, Amsterdam; 2012.
22. Kok TB, Kingma A. Herkenningsgeheugen bij kinderen [Dutch reference data for the RAVLT]. Tijdschrift voor Neuropsychologie 2009;4:42–9.
23. Rey A. L'examen clinique en psychologie. Paris: Presses Universitaires de France; 1964.
24. Strauss E, Sherman EMS, Spreen O. A compendium of neuropsychological tests: administration, norms, and commentary. Oxford (New York): Oxford University Press; 2006.
25. Smidts D, Huizinga M. BRIEF: executieve functies gedragsvragenlijst [Dutch version of the BRIEF]. Amsterdam: Hogrefe Uitgevers; 2009.
26. Centraal bureau voor statistieken; 2012. Available at www.CBS.nl. Accessed 27/02, 2021
27. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214–23.
28. Ichord R, Silverstein FS, Slomine BS, et al. Neurologic outcomes in pediatric cardiac arrest survivors enrolled in the THAPCA trials. Neurology 2018;91:e123–31.
29. Silverstein FS, Slomine BS, Christensen J, et al. Functional outcome trajectories after out-of-hospital pediatric cardiac arrest. Crit Care Med 2016;44(12):e1165–74.
30. Slomine BS, Silverstein FS, Christensen JR, et al. Neuropsychological outcomes of children 1 year after pediatric cardiac arrest: secondary analysis of 2 randomized clinical trials. JAMA Neurol 2018;75(12):1502. https://doi.org/10.1001/jamaneurol.2018.2628.
31. Verstraete S, Verbruggen SC, Hordijk JA, et al. Long-term developmental effects of withholding parenteral nutrition for 1 week in the paediatric intensive care unit: a 2-year follow-up of the PEPaNIC international, randomised, controlled trial. Lancet Respir Med 2019;7(2):141–53.
32. Aarsen FK, Paquier PF, Arts WF, et al. Cognitive deficits and predictors 3 years after diagnosis of a pilocytic astrocytoma in childhood. J Clin Oncol 2009;27(21):3526–32.
33. Brière ME, Scott JG, McNall-Knapp RY, Adams RL. Cognitive outcome in pediatric brain tumor survivors: delayed attention deficit at long-term follow-up. Pediatr Blood Cancer 2008;50(2):337–40.
34. Anderson V, Catroppa C, Morse S, Haritou F, Rosenfeld J. Functional plasticity or vulnerability after early brain injury? Pediatrics 2005;116:1374–82.
35. Verger K, Junque C, Jurado MA, et al. Age effects on long-term neuropsychological outcome in paediatric traumatic brain injury. Brain Inj 2000;14:495–503.
36. Society of Critical Care Medicine, available at https://www.sccm.org/MyICUCare/THRIVE. Accessed 15/06, 2021.
37. Topjian AA, Scholefield BR, Pinto NP, Fink EL, Buysse CMP, et al. P-COSCA (Pediatric Core Outcome Set for Cardiac Arrest) in Children: An Advisory Statement From the International Liaison Committee on Resuscitation.. Resuscitation 2021;162:351–64.
38. Sawyer KN, Camp-Rogers TR, Kotini-Shah P, Del Rios M, Gossip MR, et al. Sudden Cardiac Arrest Survivorship: A Scientific Statement From the American Heart Association.. Circulation 2020;141(12):e654–85.
39. Pediatric Resuscitation Quality Collaborative (2020) available at https://www.pedires-q.org/. Accessed 27/02, 2021