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Research Paper

Relevance of Cognitive Rehabilitation amongst Survivor Children with Critical Illnesses – A Systematic Analysis

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ABSTRACT

Cognitive Rehabilitation (CR) has been variously used in the research literature to represent non-pharmacological interventions that target the Cognitive impairments (CI). The need to address acquired cognitive impairments among children having any history of chronic illnesses like congenital heart disease (CHD), Acute Lymphoblastic Leukaemia (ALL), Epilepsy disorder etc., is inevitable. Such impairments have to be forecasted and should be pointed out for planning CR at the earliest. Published brain imaging studies and findings emphasizing CI, especially Executive Function (EF) and related psycho-social aspects, could be identified and reviewed. Based on a systematic review of the literature from 2000 - 2021, increased risk of EF deficits and psychosocial impairments were commonly found in the 3 categories and has been briefly described. Eight databases were searched, resulting in 63 studies meeting inclusion criteria for review. Clinical and research gaps in the area are discussed. In India, a very limited number of brain imaging studies and neuropsychological studies have been done indicating the CI among school-aged survivor children. Preliminary evidence shows the post-effect of chronic illness has affected cognitive functions, behaviour, academic performances and other aspects in daily life events, which indeed affected their QOL. Many studies have emphasized the relevance and the need of implementing supportive interventions like CR among survivor children.

Keywords: *Cognitive rehabilitation, Cognitive Impairments, Executive Function Deficits, Congenital Heart Diseases, Epileptic Disorder, Acute Lymphoblastic Leukaemia*

Neurodevelopmental or acquired cognitive impairments adversely impact many aspects of a child's cognitive development and is considered as one of the major morbidities associated with many chronic illnesses like CHD, ALL, ED etc (Marino, Lipkin, Newburger, Peacock, Gerdes, Gaynor, & Mahle,2012; Sanz, Wang, Berl, Armour, Cheng, & Donofrio, 2018). 6. Even though much research has shown the need for CR among survivor school aged children, the findings based on the application of CR is comparatively few, but has seen more in adult's CI like stroke, aphasia etc. Although

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neurodevelopmental impairment studies like ADHD, SLD, etc. are common, only few institutions (Adayar Institute of Cancer) in India do CR-based research among survivor children, disappointingly children with these disorders are not even getting appropriate CR in India.

CHD, one of the most common type of birth defects that affect 8 per 1000 babies born globally (Bernier, Stefanescu, Samoukovic, & Tchervenkov,2010), includes a variety of malformations of the heart its major blood vessels present at birth (http://medical-dictionary.thefreedictionary.com). Children with CHD are at high risk of having CI or neurodevelopmental impairments including attention, visual memory, language etc, or may also exhibit ADHD and ASD symptoms (Calderon, & Bellinger,2015; Rollins, & Newburger, 2014; Sterken, Lemiere, Vanhorebeek, Van den Berghe & Mesotten, 2015). School-aged children with CHD are most affected with the aspects of neurocognitive, behavioural, and psycho-social development (Calderon & Bellinger, 2015; Jacobson, Williford & Pianta, 2011; Calderon & Bellinger, 2015).

Childhood Cancer (CC) survival rates across High Income Countries (HICs), and low-income and middle-income countries (LMICs) differ substantially (Farmer, Frenk, Knaul, Shulman, Alleyne, Armstrong, & Seffrin, 2010; Ganguly, Kinsey, & Bakhshi, 2020). LMICs like India, 90% of CC has been reported with survival rates worse than HICs (Farmer et al., 2010, Bhakta, Force, Allemani, Atun, Bray, Coleman, Steliarova-Foucher, Robison, Rodriguez-Galindo, Fitzmaurice, 2019; Ganguly et al., 2020). ALL has the most reviews as it's the most common type of CC reported in India (Arora & Arora, 2016). Many findings related to ALL have shown that cognitive dysfunction is frequently seen among survivors, with its effects becoming evident mostly after few months/years. At a young age of diagnosis, high-dose treatments (cranial irradiation, use of intrathecal methotrexate) and pre-existing comorbidities are directly proportional with the risk factors of cancer-related cognitive dysfunction. These late neurocognitive effects at early age continue to compromise QOL and performance of the survivor child. (Castellino, Ullrich, Whelen, & Lange, 2014; Gandy, Scoggins, Jacola, Litten, Reddick, & Krull, 2021; Peterson, Jones, & Jacobson, 2021; Abraham, Veeraiah, & Radhakrishnan, 2021).

Epilepsy is considered to be a chronic non-communicable disease of the brain affects 50 million people worldwide (WHO, 2019), and is accompanied by temporary symptoms like loss of awareness, disturbances of movement, sensation, cognition and mood. Hence following each seizure episode, they are more prone to get physical problems, as well as psychological conditions, such as fractures, bruises, anxiety and depression. Epilepsy affects vast majority of kids, and they are at high risk to have CI's and related psychosocial problems (WHO,2019, https://www.who.int/news-room/fact-sheets/detail/epilepsy). Several contributing factors for CI are proposed, which include type of epilepsy, underlying etiologies, structural neurological abnormalities (Braakman et al., 2013; Rzezak et al., 2007; Stiers et al., 2010; Black, Schefft, Howe, Szaflarski, Yeh, & Privitera, 2010) as well as factors including early onset of seizures, longer duration, frequency of seizures, higher lifetime seizure frequency, and the type of antiepileptic drugs (Black, Shih, Sepeta, Facella-Ervolini, Isquith, & Berl, 2019; Karrasch, Tita, Hermann, & Joutsa, 2017).

These factors hinder neurological development of the child, which in turn results in higher prevalence of cognitive behavioural disturbances, long-term risk of learning problems which is directly proportional to under academic achievements, and also reported mild but

measurable decline of intellectual performance in IQ assessments (Lagae, 2006; Lodhi, & Agrawal, 2012; Black, Schefft, Howe, Szaflarski, Yeh, & Privitera, 2010).

Among the three survivor groups, EF was the commonly mentioned cognitive deficit area. EF itself has grabbed attention in recent years as it's considered to be a set of higher-order neurocognitive abilities that serve to coordinate and organize actions towards a goal, allowing the individual to adapt to new or complex situations (Bellinger, Newburger, Wypij, Kuban, & Rappaport, 2009). EF deficits reduce a child's QOL by raising difficulty in psycho-social, emotional and cognitive functioning. EF plays an important role in regulating behaviour and interference control/selective attention (Inhibitory control); the ability to work with current information in mind and mentally work with it (working memory); and the ability to perceive things differently, quickly and flexibility in adapting with the changes (cognitive flexibility), (Diamond, 2013). These abilities develop at some point in childhood, simultaneously with some developmental transitions and demanding situations. One of those demanding situations is the transition from elementary into middle-level schools, which has the capability to noticeably disrupt kid's educational and social trajectories.

Parent reports reveal that middle-school (9 - 13 years of age) children having weaker EF skill tend to have more behavioural problems and less regulatory control, whereas teachers reported more educational and behavioural problems in elementary school age students (5 -7 years of age). Middle-school children having poor EF skills with less external support report to have substantial adjustment issues in academic and in behavioural aspects (Jacobson, Williford, & Pianta, 2011).

Current study focuses on the systematic review of commonly highlighted cognitive impairments specifically, the presence of EF deficits among school-aged children who survived chronic illnesses and to understand its effect on daily life activities (school performances and psychosocial domains). The intention was to bring attention to researchers on implementing child-based cognitive interventions. No review protocol was used to conduct the study.

METHODS

Eligibility criteria

For inclusion in this review, studies fulfilled the following eligibility criteria:

- ***Participants:*** School aged children, aged from 5 to 17 years
- ***Exposure:*** measurement of any history of chronic illness and who underwent related treatment.
- ***Outcome:*** CI, poor academic achievers, poor psycho-social functioning and QOL assessed by validated instruments.
- Most studies were from peer-reviewed journals with full text available in English.

Search Strategy

The data Wiley Online Library, Elsevier, Taylor & Francis, Lancet Oncology, Oxford Academia, American Academy of Paediatrics, Google Scholar & South Asian Journal of Cancer were searched for the studies, on April 1st to October 15th, 2021; the duration considered was from 2000 to 2021.

The search strategy terms included were "CI, neuropsychological impairments", "children, school aged children"," Cancer survivors' children, paediatric cancer", "CHD", "epilepsy, seizure disorder ", "EF deficits, Daily life functioning", "Academic performance "," behavioural issues, psycho-social factors" and "QOL".

Additional studies were identified by screening the systematic reviews included in the search results. All studies identified in the search were important and few were eliminated.

Data Extraction

Most papers from the automated database searches were collated using the Mendeley reference management software. After duplicates were deleted, screening was conducted to ensure that studies fulfilled the eligibility criteria. Initially the papers were screened based on title and abstract, and the remaining was screened on full text.

The Screening process comprised of:

1. Characteristics of Articles (Year of publication, review & meta-analysis study, Experimental control group, randomized controlled studies, uncontrolled pre-post studies, Neuro-psychological assessment and Brain imaging studies, epidemiology, articles suggesting any remedial or intervention for survivor children, and outcomes measuring EFs).
2. Characteristics of participants (including age, years of education, diagnosed with chronic illness, Survivors of chronic illness and if underwent any high dose treatment or surgeries).
3. Type of chronic illness (ALL, CHD, Epilepsy disorder).
4. Cognitive domain analysed (CI in general & executive functions in specific).
5. CI related Psychosocial and behavioural deficits.

RESULTS

The literature search yielded 85 articles from 8 databases of which 15 duplications were later removed of the remaining 70 articles, 10 were removed, leaving 60 papers. Most common reason for ineligibility was the age range and the type of differed illnesses.

An overview of Systematic Analysis and mostly used research designs are listed in the Table 1 & 2.

Table 1: An overview of Systematic Analysis done in each chronic illness categories

Chronic Illness	No. of studies	Database	Year of publica-tion	CI	Samples	Impact on daily living
CHD	20	ELSEVIER CAMBRIDGE PRESS CIRCULATION BMJ	2007 2008 2010 2011 2014 2015 2016 2017 2018	Sustained attention, Divided attention, EF (monitoring, WM,CF, Problem Solving, Verbally mediated EF skills, visuo-spatial skills, Planning / Organization P/O,	School-aged children, Adolescents , Survivors (aged between 8-19 years old)	A range of cognitive, learning, motor, IQ, school competency, school QOL and psychosocial vulnerabiliti

		TAYLOR&FRANCIS WOL AAP PUBLICATION	2019 2020 2021	and Metacognition), Delay in early speech/language milestones , Cognitive difficulties in language task, Memory problems (visual memory) Social Problems, weaker school competence , visuospatial processing deficits, Aggressive behaviour, Low-average IQ range		es are affecting school-aged children with CHD across the lifespan
ALL	18	AUTHOREA, TAYLOR&FRANCIS WOL, THIEME, PMC, WILEY, ELSEVIER, SPRINGER, CANCER RESEARCH, STATISTICS AND TREATMENT, OXFORD, ACADEMIC, LANCET	2014 2015 2016 2017 2018 2019 2021	Attention, Sustain attention, Information Processing Speed, Fine Motors, EF (CF, WM /verbal WM, RI, and other EF like meta-cognitive, perceptual reasoning, P/O skills etc), Motor Control and Visual-Motor Integration, Low-Average IQ range	Aged range between 0-21yr old (As longitudinal study was included age limit has crossed the 17 years of age)	Neuro-behavioral problems, scholastic problems, psychosocial problems Oppositional behaviors and psychiatric morbidity exhibited in a significant minority of ALL survivors.
Epilepsy	22	ELSEVIER WOL SAGE JOURNALS NCBI PMC HEALIO TAYLOR FRANCIS WOL CAMBRIDGE UNIVERSITY PRESS INTERNATIONAL JOURNAL OF ADOLESCENT MEDICINE AND HEALTH	2001 2002 2006 2007 2010 2011 2012 2013-cros 2014-2015 2016 2019 2020	Non-verbal and Verbal attention, Verbal Memory, Processing Speed, WM, CF, Planning, verbal fluency VF and visuo spatial VS skills, Low-average IQ range EF-like Monitoring, WM, CF,PS, Verbally mediated EF skills, visuo-spatial skills, P/Oskills, and Metacognition	Age between 4.6 years to 18 years old	Long-term risk of learning problems, Under academic achievements, behavioral problems, social and academic failure were explicit among children having a history of epilepsy.

Table 2: Mostly used research designs in each chronic illness category

Type of Chronic illness	**Research Design**
CHD	Systematic Review-Meta Analysis Pre-post experimental design Randomized Controlled design Primer study evidence based Longitudinal Study
ALL	Experimental Design- Controlled design Systematic Review Longitudinal Study Cross Sectional Study
Epilepsy	Review Study Experimental Design- without Controlled design Randomized Double -Blind Trial Experimental Design- with Controlled design- Longitudinal Study Cohort study

DISCUSSION

Neurocognitive deficits, initially subtle in survivors, can progress over time and have an adverse impact on long-term functional outcomes and QOL (Kunin-Batson, Kadan-Lottick & Neglia, 2014; Chidambaram, & et al.,2019). As survival rates improved and neurotoxicity declined, survivors of ED, CHD, and ALL treated with chemotherapy alone, continued to demonstrate long-term alterations in brain development and function, that corresponds with neurocognitive deficits in domains of attention, executive function, and processing speed (Braakman et al., 2013, Van der Plas, et al., 2017; Chidambaram, & et al.,2019, Gandy, et al., 2021; Gutierrez, et al.,2021) and other cognitive domains.

CHD*:* A primer study on CHD done by Cassidy, Ilardi, Bowen, Hampton, Heinrich, Loman, & Wolfe (2018) mentioned that children with CHD (d-TGA, dextro-Transposition of the Great Arteries and HLHS, Hypoplastic left heart syndrome) who underwent surgery scored on IQ from Average to low-average range. School-age children with mixed CHD consistently demonstrated difficulties with sustained attention & executive aspects of attention including divided attention; EF (conflict monitoring), memory problems (visual memory), delay in early speech /language milestones and found deficits were predominant in visuo-spatial processing. In 2008, Miatton, et al., studied parental report findings, which revealed that children with CHD have social problems, weaker school competence and more aggressive behaviour. However, the presence of neurocognitive impairment in children with CHD has been identified over the last two decades.

The most commonly reported CI were in the EF domain like monitoring, working memory, CF, problem solving, verbally mediated EF skills, visuo-spatial (VS) skills, planning / organization (P & O), and Metacognition (M.Cog) (MacAllister, Vasserman, Rosenthal, & Sherman, 2014; Feldmann, Bataillard, Ehrler, Ullrich, Knirsch, Gosteli-Peter,& Latal, 2021; Cassidy, White, DeMaso, Newburger, & Bellinger, 2015; Sanz, Berl, Armour, Wang, Cheng, & Donofrio, 2017; Sanz, Wang, Berl, Armour, Cheng, & Donofrio, 2018; Gerstle,

Beebe, Drotar, Cassedy & Marino, 2016; Feldmann, Bataillard, Ehrler, Ullrich, Knirsch, Gosteli-Peter, & Latal, 2021). School-aged children with CHD are most commonly affected with the aspects of neurocognitive, behavioural, and psycho-social development (Calderon & Bellinger, 2015; Jacobson, Williford & Pianta, 2011; Calderon & Bellinger, 2015).

Cassidy, et al., 2018, has pinpointed a higher prevalence of special education categories of intellectual disability, sensory impairment, other health impairment, significant developmental delay, and specific learning disability (SLD) among school-age (8 years old) children with CHD.

ALL: The cognitive deficits are analyzed by using both brain imaging studies and neuropsychological assessments. Many recent brain imaging studies have shown the reduced brain volumes in the frontal and parietal white matter, temporal and occipital grey matter, and neurocognitive impairments in ALL survivors treated with cranial radiotherapy and chemotherapy (Follin, Erfurth, Johansson, Latt, Sundgren, Osterberg, & Bjorkman-Burtscher, 2016; van der Plas, Schachar, Hitzler, Crosbie, Guger, Spiegler, & Nieman, 2017). Similar studies conducted on long term ALL survivors have shown a thicker cortex and higher activity in frontal brain regions associated with EF, and a higher plasma concentration of methotrexate was proportional to executive dysfunction (Krull, Cheung, Liu, Fellah, Reddick, Brinkman, & Hudson, 2016).

Although Prophylactic treatment has improved survival rates, over the years neurotoxic effects of chemotherapy and cranial radiation therapy have displayed long-term alterations in brain structure and function, which contribute to lifelong neurocognitive late effects in paediatric survivors (Chidambaram, Elangovan, Mahajan, Ganesan, & Radhakrishnan, 2019; Kunin-Batson,Kadan-Lottick,& Neglia, 2014; Chidambaram, & et al.,2019; Gandy, Scoggins, Jacola, Litten, Reddick, & Krull, 2021).

The neuropsychological assessments demonstrated significant impairment in IQ, and commonly found other neurocognitive domains where attention, sustained attention, WM, response inhibition –(RI), information processing speed, fine motors, particularly in EF, motor control and visual-motor integration were explicit. Gradually the late effects have also overridden to the adolescent phase and has shown deficits mostly in immediate memory and verbal WM. This CI was also accompanied with neurobehavioral problems, oppositional behaviours and psychiatric morbidity exhibited in a significant minority of ALL survivors (Iyer, Balsamo, Bracken, & Kadan-Lottick, 2015; Krull, Cheung, Liu, Fellah, Reddick, Brinkman, & Hudson, 2016; Follin & et al., 2016; Van der Plas, et al., 2017; Liu, Cheung, Brinkman, Banerjee, Srivastava, Nolan, & Krull, 2018).

Several studies demonstrated higher impairment in different EF domains, especially in three main core EF domains - CF, WM, RI, and other EF like meta-cognitive, perceptual reasoning, P&O etc (Gutierrez, Filippetti, & Lemos, 2021; van der Plas, et al., 2017; Follin, et al., 2016; Winter, Conklin, Tyc, Stancel, Hinds, Hudson, & Kahalley, 2014). A large series of cancer survivors from India, showed scholastic problems and psychosocial problems in around 43% and 57% of the cohort, respectively (Kurkure, Achrekar, Uparkar, Dalvi, & Goswami, 2003; Vishwa, Das, Seth, Sapra, Siri, Meena, & Vishnubhatla, 2021).

Epilepsy*:* Studies show, according to the types of seizure disorder the profile of CI differ; not every epileptic child must illustrate deficit in all the cognitive areas. In 2015, Park., Shah

and Jammoul conducted a study on most common paediatric epilepsy syndromes in India and the results include BRE, CIOE, CAE, and JME. Many evident findings have shown its connection to having CI and behavioural problems (Kwon, Seo, & Hwang, 2012, Germanò, Gagliano, Arena, Cedro, Vetri, Operto, & Roccella, 2020, Shinnar, Cnaan, Clark, Dlugos, & Hirtz, 2017). The most reported CI were in EF domains, as same as mentioned in CHD (Riccio, Pliego, Cohen, & Park, (2015).

Brain imaging studies have also shown supporting evidence on indicating structural and functional abnormalities. Dinkelacker, Xin, Baulac, Samson, & Dupont, S. (2016); Braakman, Vaessen, Hofman, Debeij-van Hall, Backes, Vles, & Aldenkamp, 2011), studied how the TLE and FLE differ with respect to localization and functionality. Empirical evidence has shown the association between FLE and cognitive domains like attention and inhibition problems, social cognitive problems, and aggression (Riva, Saletti, Nichelli, & Bulgheroni, 2002., Braakman, et al., 2011).

van den Berg, Lydia; de Weerd, Al; Reuvekamp, Marieke; Hagebeuk, Eveline; van der Meere, Jaap (2018) has reported high correlation between EF and behavioural functioning, specially FLE could lead to EF problems, which results in behavioural problems, social and academic failure (Helmstaedter, 2001; Braakman, et al., 2011; Sun, & Buys, 2012, Smith, 2016.)

Decades of findings reveal, somehow a range of cognitive, learning, motor, IQ, school competency, school QOL and psychosocial vulnerabilities are affecting school-aged children with chronic illness across the lifespan (Kurkure, et al., 2003, Gerstle, Beebe, Drotar, Cassedy, & Marino,2016; Smith, 2016. Ilardi, Sanz, Cassidy, Sananes, Rollins, Shade, & Bellinger, 2020). Numerous studies have highlighted that EF plays a crucial role in various day-to-day life settings and has highlighted the need for neuropsychological follow-up (Sanz, et al., 2017, Diamond, 2013). Hence many researchers suggest early intervention or support for EF skill development (Sanz, et al., 2018, Cassidy, et al., 2018, Liu, et al., 2018) and behavioural management for monitoring the child's progress in education, neuro-cognitive and psycho-social domains, thereby enhancing the skills to engage successfully in independent, purposive, self-directed, and self-serving behaviour.

The crucial gap in the research found was regarding the implementation of preventive or supportive intervention strategies for these important cognitive morbidities. Previous studies on evidence-based interventions have shown promising results in other paediatric populations (ADHD /SLD), strongly suggesting a well-structured cognitive intervention or CR, which might benefit the growing population of children who survived chronic illness. Researcher has tried to bring realization on the chances of CI that are commonly found among survivors during their critical developmental period, which can be extended in future investigations.

CONCLUSION

Many findings have revealed that EF impairments are one of the most prominent CI commonly seen in all 3 categories. Numerous studies have been conducted to investigate the deformities and challenges happening in the cognitive and psycho-social aspects, albeit very few have conducted applied research on showing the effectiveness of CR or introduced a specific model for approaching survivor children. Hence suggesting future researchers to

investigate more into the applied CR rather than just identifying the deficit areas and claiming the need for intervention.

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Conflict of Interest

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