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REVIEW

Factors Affecting Neurocognitive Function in Children with Chronic Kidney Disease: A Systematic Review

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Purpose: In children, chronic kidney disease (CKD) has been known to affect neurocognitive function which can impair the quality of life. This study aims to determine the factors and treatment modalities which might affect neurocognitive function in pediatric population with CKD.

Patients and Methods: A systematic review was done using 3 electronic databases: PubMed, ScienceDirect, SpringerLink, and carried out based on PRISMA guidelines. Our review included articles published in the last 10 years (2011–2021) in English, on children aged 0–18 years with CKD. Factors affecting the children's neurocognitive function were assessed.

Results: Eight articles were included in this study. Three articles reported that parent's education, especially maternal education affect the neurocognitive function of children with CKD. In relation with modalities, in general, children with CKD who had kidney transplant had a better neurocognitive outcome. A longer duration of hemodialysis (HD) was associated with poorer neurocognitive outcomes. Other factors that can affect the neurocognitive function included depression, a history of abnormal births, seizures, and hypertension.

Conclusion: In children, CKD might cause neurocognitive function disorders through various complex and interconnected mechanisms. Further studies are needed to determine the mechanism and prevention of neurocognitive disorders, as well as the best choice of therapeutic modality to improve both kidney function and neurocognitive function in children with CKD.

Keywords: chronic kidney disease, neurocognitive function, children

Introduction

Chronic kidney disease (CKD) is an irreversible kidney disorder, anatomically and functionally.[1] In general, the prevalence of CKD is about 18 patients out of 1 million children.[2] Based on data from a large study by the ItalKid Project from a population-based register in Italy, consisting of children and young adult population less than 20 years of age, the incidence of CKD is 12.1 cases and the prevalence is 74.7 cases out of 1 million population of people younger than 20 years old. This study also found that CKD in the pediatric population is mostly caused by hypoplasia and dysplasia, with or without other malformations of the urogenital system.[3,4] Other kidney diseases might also cause CKD, such as nephrotic syndrome or glomerulonephritis, urinary obstruction or infection.[5]

In children, chronic kidney disease has been known to affect neurocognitive function due to uremia and anemia, especially in stage five, which can affect brain metabolism, myelination of neurons and synapse development.[6] The results of the studies regarding this topic varied from one study to another. Several studies found a lower Intelligence Quotient (IQ) in children with CKD compared to the healthy group. Another study showed no significant differences in memory (verbal and non-verbal) function in children with and without CKD. Other studies had stated that there were deficits in auditory assessment, verbal working memory, and emotional recognition. Intelligence Quotient scores in children who had chronic hemodialysis (HD) were lower than in children with moderate CKD or children who had kidney transplantation.[6]

Many interventions had been carried out to prevent further decline in kidney function in children with CKD. In addition to providing conservative therapy at an early stage, renal replacement therapy (RRT), including hemodialysis (HD),

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peritoneal dialysis (PD), and kidney transplantation, are some of the modalities that can be performed in children with stage five CKD (terminal renal failure). One study found that health-related quality of life (HRQOL) was better in children with CKD with kidney transplantation than PD and HD.[7] It is known that neurocognitive function is one of many components that can affect a person's Health-Related Quality of Life (HRQoL); thus, neurocognitive function can be affected indirectly by the therapeutic modality given to the patient.[8,9] In patients with CKD undergoing dialysis, the prevalence of neurocognitive disorders ranges from 30% to 70%. In general, 30% of patients with CKD had poor cognitive performance scores (about one standard deviation lower than the control group), with 18% having memory deficits and 30% having executive function deficits.[10] This is particularly important in the children, because the brain still developed rapidly. On the other hand, impaired neurocognitive function can affect the quality of life of children in the future.

This systematic review was made to find out about factors that can affect neurocognitive function in children with CKD. Hopefully, through this study, we can provide a deeper description and understanding of the relationship between CKD and neurocognitive function in children with CKD.

Materials and Methods

Search Strategy

Literature search was performed using keywords with a combination of Boolean connectors ("CHILDREN" OR "PEDIATRIC") AND ("END STAGE RENAL DISEASE" OR "CHRONIC KIDNEY DISEASE" OR "CKD" OR "ESRD" OR "ESKD") AND ("NEUROCOGNITIVE") AND ("RENAL TRANSPLANT" OR "KIDNEY TRANSPLANT" OR "HEMODIALYSIS" OR "PERITONEAL DIALYSIS" OR "RENAL REPLACEMENT THERAPY") with various combinations. The systematic review was carried out based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The authors used articles from 3 databases: PubMed, ScienceDirect, and SpringerLink. The population of children with CKD and the therapeutic modalities were assessed. The systematic review also assessed factors influencing neurocognitive function in children with CKD.

Eligibility Criteria

The studies included were limited to articles published in the last 10 years (2011–2021), in English, included children aged 0–18 years with CKD who were treated either conservatively or with RRT, and whose neurocognitive function was assessed. The exclusion criteria were researches using qualitative methods, abstracts from national/international conferences, guidelines, case reports, commentaries, and review articles.

Data Extraction

The data was extracted from the literatures which met the aforementioned criteria. For continuous variables, the number and percentage of variables were assessed. The findings were also described further in narratives. Some findings in the form of categorical variables were described in numbers. The main outcomes assessed were impaired neurocognitive function in children with CKD, the therapeutic modalities used, and factors that might affect neurocognitive function in children with CKD.

Data Analysis

All studies which met the criteria were identified using the selected keywords. Then, title screening was done, followed by abstract screening. Complete article screening was done studies that met the inclusion criteria and did not meet the exclusion criteria.

Study Quality

The validity of the included studies was assessed using the Critical Appraisal Skills Program (CASP) tool for the cohort studies and Center for Evidence Based Management (CEBMa) for the cross sectional studies.[11,12] These tools consisted of several checklist based on the research methods used and were used to assess the trustworthiness, relevance, and results of the published papers.

Results

Based on PRISMA guidelines, the article review process is illustrated in Figure 1. From the search results, 561 articles were found after articles and duplicated titles were removed from the online database, consisted of 412 articles from PubMed, 51 articles from ScienceDirect, and 98 articles from SpringerLink. After screening the titles and abstracts of the articles, there were 14 articles, and after full article review was done, eight articles that met the criteria were obtained. Two articles were literature reviews, five did not contain the required data, and one did not use children as the sample in their research. The search results article findings are summarized in Table 1.

From this study, we found that several factors that affect the neurocognitive function of children with CKD include the parent's education, especially maternal education in the study of Zyada et al,[13] Kogon et al,[14] and Molnar-Varga et al.[15] In relation with the modalities, studies from Johnson et al,[16] and Molnar-Varga et al[15] showed that in general, children with CKD children with kidney transplantation had a better neurocognitive outcome. In children with CKD, a longer duration of HD was also found to be associated with poorer neurocognitive outcomes in a study by Popel et al,[17] Zyada et al,[13] and Molnar-Varga et al.[15] In a control study, patients with renal impairment showed poorer neurocognitive function than normal children by Zyada et al,[13] Johnson et al,[16] and Molnar-Varga et al[15] Several factors that can affect the neurocognitive function of children with CKD include depression, history of abnormal births, seizures, and hypertension. From all included studies, it was found that the neurocognitive function domains which affected by CKD varied, but generally, the affected domains were attention, visual-spatial, visual working memory, verbal function, and executive function. The number of the boys was higher in the entire group of patients with CKD when compared to the number of the girls.[13–20]

The stages of CKD in the included articles in this systematic review were CKD stages 1–4, dominated by CKD stage 5 patients.

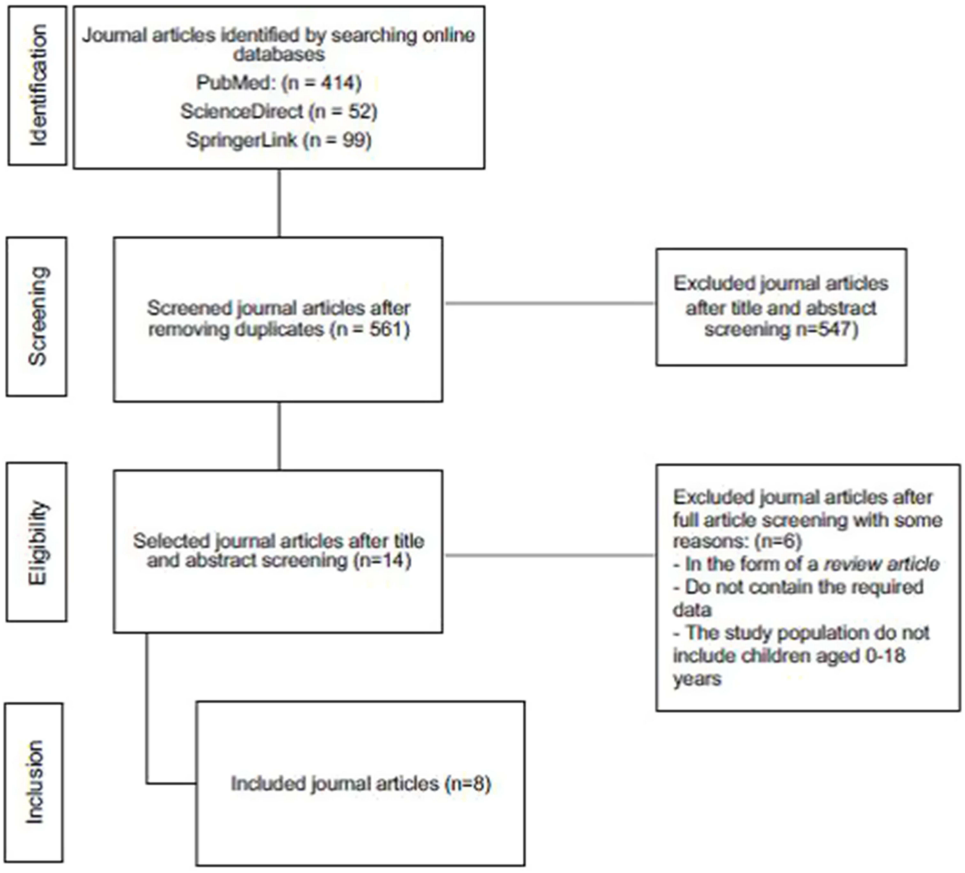

Figure 1 Journal article search flowchart.

Table 1 Summary of Journal Findings

The Research Result	CKD Stage	Theurapeutic Modalities	Neurocognitive Assessment Methods	Sample	Research Sites	Research Methods	Country	Year	Researcher	Title
• School performance was worse in the HD group than the post-kidney transplant group and the control group. • There was a negative correlation in the HD group between the duration of HD and the WISC III subtest scores, • There is a positive correlation between post-kidney transplant duration and WISC III subtest scores • Low educated parents were more in the post-kidney transplant group (60%) than in the transplant group (25%), and the control group (5%)	Stage V	HD Kidney Transplant	Wechsler Intelligence Scale for Children Third Edition (WISC III)	60 children aged 6–16 years	Egypt	Cross Sectional	Egypt	2017	Zyada et al[11]	Assessment of cognitive functions in children on regular hemodialysis and after renal transplantation[11]
• Longer dialysis duration is associated with worse outcome • HD is associated with poorer developmental outcome • Age at transplantation is not significantly associated with neurologic outcome • Neurocognitive outcome is better than data in the past 2–3 decades.	Stage V	Peritoneal dialysis in 11 patients HD continued with PD in 4 patients Followed by kidney transplant in all patients	Wechsler Preschool and Primary Scales of Intelligence–3rd edition Beery- Buktenica Developmental Test of Visual-Motor Integration (VMI; 5th edition)	15 patients who received transplant before the age of 5 years	Canada (Alberta)	Prospective Cohort	Canada (Alberta)	2019	Popel et al[15]	Neurocognitive and functional outcomes at 5 years of age after renal transplant in early childhood[15]

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Depression in patients with CKD shows that there are functions that are affected by neurocognitive examination in the domains of attention, visual memory, visual-spatial, visual working memory, problem solving.	Stage I–IV Srage V	Conventional 51 patients HD 2 patients Transplant 18 patients	Wechsler's Abbreviated Scales of Intelligence (WASI) Conner's Continuous Performance Test II (CPT II) Wechsler Intelligence Scale IV (WISC IV) Wechsler Memory Scale Third Edition (WMS III) Delis Kaplan Executive Function System (D-KEFS) Behaviour Rating Inventory of Executive Function (BRIEF)	1 CKD patients and 64 controls aged 8–25 years	United States (Philadelphia)	Cross Sectional	United States (Philadelphia)	2019	Kogon et al[12]	Depression and neurocognitive dysfunction in pediatric and young adult chronic kidney disease.[12]
• Abnormal birth history and low maternal education are significantly associated with lower IQ • History of seizures related to worse executive function	Stage I–V	NA	Wechsler's Abbreviated Scales of Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI III) Kiddie Conners' Continuous Performance Test for ages 48–71 months (K-CPT)	124 preschool children with CKD	United States (Philadelphia, Kansas)	Prospective Cohort	United States (Philadelphia, Kansas)	2016	Hooper et al[16]	Neurocognitive, social-behavioral, and adaptive functioning in preschool children with mild to moderate kidney disease.[16]

(*Continued*)

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Table 1 (Continued).

The Research Result	CKD Stage	Theurapeutic Modalities	Neurocognitive Assessment Methods	Sample	Research Sites	Research Methods	Country	Year	Researcher	Title
• FSIQ, academic function, and executive function are lower than the control group • Shorter duration of dialysis and younger age at transplant are associated with better outcomes in executive function, memory, and academic achievement	Stage V	PD in all patients at early treatment, then 2 patients changed to HD	Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV) Wechsler Individual Achievement Test Second Edition—Abbreviated (WIAT-II- A) Wide Range Assessment of Memory and Learning, Second Edition (WRAML2) Behavior Rating of Executive Functioning (BRIEF)	12 patients with ESRD in the first 16 months	United States	Cross Sectional	United States	2013	Johnson et al[14]	Long-term neurocognitive outcomes of patients with end-stage renal disease during infancy.[14]
• The group with CKD had lower scores in all neurocognitive domains, with statistically significant domains were attention, memory (including verbal, visual, short-term memory, working memory), visual spatial, inhibitory control • Neurocognitive performance was better in patients with higher eGFR, with significant differences in the domains of attention, visual spatial, visual working memory • Higher blood pressure is associated with poorer performance in language and verbal memory	Stage II–V	Conventional Hemodialysis Kidney Transplant	NA There are 11 domains assessed: attention, language, verbal memory, verbal working memory, visual memory, visual spatial, visual working memory, executive function, inhibitory function, problem solving, set shift	162 patients aged 8–25 years	United States (Philadelphia)	Cross Sectional	United States (Philadelphia)	2015	Ruebner et al[17]	Neurocognitive dysfunction in children, adolescents, and young adults with CKD.[17]

• The duration of CKD affects the executive function of the inhibitory domain and concentration • Higher family income and better maternal education showed better working memory component assessment results	NA	Conventional	Conner's Continuous Performance Test II (CPT-II) Delis-Kaplan Executive Function System Tower Task (DKEFS) Wechsler Intelligence Scale for Children Fourth Edition (WISC IV)	340 children aged 6–21 years	North America	Cross Sectional	North America	2015	Mendley et al[18]	Duration of chronic kidney disease reduces attention and executive function in pediatric patients.[18]
• Transplant patients, compared to controls, have lower IQs in all aspects, and have better scores on verbal skills, with the lowest skill on cognitive efficiency. • Younger age at started dialysis and longer cumulative dialysis time associated with poorer neurocognitive outcome in children • Higher maternal education is associated with Woodcock-Johnson Cognitive Ability Test – International Edition (WJIE) scores	Stage V	Kidney Transplant	Woodcock-Johnson Cognitive Ability Test – International Edition (WJIE)	35 children aged 6–18 years who received kidney transplants	Hungary	Cross Sectional	Hungary	2016	Molnar-Varga et al[13]	Neurocognitive functions of pediatric kidney transplant recipients.[13]

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In a study by Ruebner et al, lower stage of CKD or those with higher Glomerular Filtration Rate (GFR) had an effect on better neurocognitive function in patients with CKD.[16]

In the study of Popel et al, it was found that although the overall neurocognitive outcome in patients with CKD was not good, in that study, the neurocognitive outcome of children with CKD was better than 2–3 decades ago. This might be related to the development of therapeutic modalities for children with CKD.[17]

Discussion

According to Kidney Disease Improving Global Outcome (KDIGO), the definition of CKD is an abnormality of kidney structure or function that lasts for more than three months, with implications for the patient's health. CKD is classified by the etiology, GFR category, and albuminuria category.[17] Based on the Kidney Disease Outcomes Quality Initiative (KDOQI), CKD can be defined as kidney disease with one of the following two criteria, namely (1) kidney damage for at least three months with or without decreased glomerular filtration rate (GFR), or (2) patients with GFR less than 60 mL/min/1.73 m2 for three months with or without renal impairment. However, there are two exceptions in children. The minimum three-month criteria for the first criterion does not apply if the child has persistent kidney damage. The second criterion does not apply to children <2 years of age because GFR <60 mL/min/1.73m2 can be considered normal due to suboptimal kidney function in children this age. In children, chronic kidney disease can cause many implications, such as failure to thrive, electrolyte disturbances, anemia, decreased quality of life, and impaired neurocognitive function.[1] Neurocognitive function decline in children with CKD is caused by various factors that may be interrelated. Several domains which consistently affected by CKD from several studies included in this systematic review were attention, visual-spatial, visual working memory, verbal function, and executive function. The presence of attention disorder could affect a child's ability to acquire new abilities and perform previously learned abilities. These attention disturbances may affect other neurocognitive domains, such as memory and verbal function.[21]

There were several clinical biomarkers which had been known to affect neurocognitive function from previous studies in children with CKD. Elevated blood pressure was associated with lower full scale IQ (FSIQ) and set shifting error in executive function. Anemia, proteinuria, longer duration of CKD, lower GFR and some certain genomic variants were also associated with lower IQ in children. More interestingly, correlation between neuroimaging studies and cognitive function in children with CKD was also found in a recent study. Using CT imaging, global cerebral atrophy, silent white matter infarcts, lower cerebral density, and ventriculomegaly were found more in children with CKD compared to normal children. When the imaging was done using Functional Magnetic Resonance Imaging Study, cerebral blood flow to the brain was also found to be disrupted, and this might be the one of the complex mechanisms that underlay the cognitive function decline in children with CKD.[22]

In one of the articles included in this systematic review, Kogon et al found that depression was one of the factors that affect neurocognitive function in children with CKD. This finding is in line with another finding in a systematic review by Baune et al conducted on a general population of adolescents and young adults where depression was associated with the domains of executive function, verbal, and visual memory.[23]

The included studies found that high blood pressure in patients with CKD would affect their neurocognitive function. Hypertension could cause and became a marker of CKD severity in children. It was also found to increase the risk factor for cardiovascular disorders in the future. In patients with CKD, the pathophysiological mechanism of hypertension was due to abnormal vascular regulation in conditions of fluid overload, increased cardiac output, and increased peripheral vascular resistance. The activation of the renin-angiotensin-aldosterone system (RAAS), possibly due to renal tissue damage with hypoperfused areas could cause vasoconstriction, water and salt retention, and sympathetic nerve hyperactivity.[24] Although the physiological basis for decreased neurocognitive performance in children with hypertension was unclear, there was evidence of changes in cerebrovascular reactivity in children. Cerebrovascular reactivity was an important physiological mechanism for maintaining constant blood pressure and was defined as the capacity of cerebral blood vessels to dilate or constrict to different stimulation. In addition, cerebrovascular reactivity was an important biomarker of brain vascular reservoir. Hypertension might affect small blood vessels, then cause vascular remodelling and disturbances in the regulation of cerebral blood flow. Cognitive processes stimulate the regional distribution of blood flow, providing metabolic support to active neural regions. Hypertensive conditions might interfere

with this normal blood flow distribution and might also reduce the ability to increase blood flow in response to increased neuronal activity, known as the vascular hypothesis of cognitive dysfunction. This process might underlie the occurrence of impaired cognitive function in individuals with hypertension. This study result is in line with other studies by Lande et al, and Ostrovskaya et al, regarding hypertension in children, which showed that a decrease in executive function was associated with impaired cerebrovascular reactivity.[25,26]

The accumulation of toxic urea in neurons is also a factor that may cause neurocognitive disorders, seizures, and status epilepticus in patients with CKD. An animal study by Mazumder et al showed that there was an accumulation of Guanidinosuccinic acid in CKD patients and an increase in adenine which then caused clonic seizures, status epilepticus, and hippocampal neurons damage. In addition, electrolyte imbalance in the brain and peripheral nerves can cause neurotransmission disturbances, which indirectly indicates that seizures could be a marker of brain damage and resulted in impaired neurocognitive function in patients with CKD.[27] In CKD, it was also found that the blood–brain barrier will change and become more permeable, so that harmful components could enter the brain more easily. Blood–brain barrier damage was partly mediated by systemic inflammation, which is one of the causes of CKD. In systemic inflammatory conditions, cytokines and chemokines, including interleukins will enter brain tissue and cause neuronal and astrocyte damage. Uremic conditions could also cause damage to the blood–brain barrier. Increased urea to a particular concentration could damage the tight junction epithelium in the intestine and the blood–brain barrier, leading toxic materials entering the blood vessels. Uremia was also associated with the emergence of oxidative stress. It could cause conversion from nitric oxide to toxic peroxynitrite, and afterwards, lipid peroxidation and neuronal damage. In animal experiments, pyknosis and apoptosis were found in hippocampal neurons under uremic conditions. Decreased renal homocysteine clearance in CKD could cause an increase in homocysteine, and its conversion to homocysteic acid would activate of the N-Methyl-D-Asparate receptor, causing neuronal toxicity. Homocysteic acid might also cause endothelial dysfunction and a pro-thrombotic effect. Impaired clearance of drugs consumed due to kidney damage and increased penetration into the blood–brain barrier are also factors that play a role in neurotoxicity and cognitive decline in CKD.[28]

In patients with CKD, it is known that the occurrence of fibrosis in the renal interstitium caused changes in the extracellular matrix (ECM) which then changed the structure of the kidney. The primary mechanism leading to the accumulation of ECM deposition is found to be the proliferation and activation of interstitial fibroblasts to myofibroblasts and increased ECM synthesis and release. Erythropoietin (EPO) production would be affected, and this mechanism is essential in the disturbance of hematopoiesis process. Production of EPO occurs interstitially in fibroblast-like cells in the renal cortex and medulla. In CKD, cells that produce EPO will experience progressive damage, accompanied by fibrosis in the patient's kidneys leading to anemia.[29] In a study by Agrawal et al, a decline in cognitive function in adult patients with anemia was found. In addition, cognitive function was also associated with hemoglobin levels in adult patients who previously had an intact neurocognitive function. This may be related to a decrease in the number of red blood cells and oxygen-carrying capacity, which impairs neurocognitive function.

Low birth weight (LBW), prematurity, and growth disorders are markers of disturbances in the intrauterine environment. There is a correlation between birth weight and the number of glomeruli, density, volume, size, and filtration rate in the kidney after birth. The number of nephrons and birth weight were also found to be related with increased blood pressure and later in life, the occurrence of CKD.[30] In conditions where the number of nephrons is reduced, a person will initially be able to maintain a normal GFR. The size of the nephrons will enlarge to increase the surface area necessary for the kidneys to work. Overtime, this adaptive response will become harmful. An increase in the surface of the glomerulus will cause sodium retention and systemic hypertension, and glomerular hyperfiltration will interfere with the autoregulatory mechanism of the kidney, causing intraglomerular hypertension and proteinuria. This process will cause the nephrons to become sclerotic and lead to a decrease in the number of nephrons and an even more severe hyperfiltration process in the remaining nephron causing more nephron damage and kidney damage in a repeated cycle. In premature infants, developing nephrons are susceptible to maldevelopment and dysfunction in the extrauterine. Premature infants are found to have reduced nephron width and more mature-looking glomeruli than normal infants, indicating that nephrogenesis had stopped or post-natal maturation was faster than term infants. Premature infants also have a larger glomerular volume (indicating a glomerular hyperfiltration process), and approximately 13% of their glomerulus have abnormal histology, with dilated Bowman's space and less glomerular tuft.[31]

As described in the previous paragraph, the mechanism that causes neurocognitive disorders in patients with CKD who have a history of low birth weight or prematurity may be due to hypertension and uremia. However, the condition of low birth weight and prematurity itself can cause neurocognitive disorders. Lower IQ scores in children with LBW were associated with structural changes in the brain compared to children who born with normal birth weight in a study by Sripada et al[32] Another study by Joseph et al showed a decrease in neurocognitive function in infants born with extremely low birth weight and gestational age <28 weeks, where neurocognitive deficits was found in ten years old children, and this finding supported the previous study.[33]

There is a risk of brain structural abnormalities and neurocognitive disorders in patients undergoing dialysis. Structural abnormalities include brain atrophy, silent brain infarction, white matter hyperintensity, and *leukoaraiosis* (subcortical injury to white matter due to loss of axons and myelin secondary to ischemic injury). Some factors that are thought to cause this include rapid changes in blood pressure during dialysis. Autoregulatory mechanism which is disrupted due to vascular disorders in hypertensive conditions in CKD patients can cause intradialysis hypertension.[34] In a study by Sandwijk et al, it was found that through MRI a year after transplantation, there was an increase in the volume of white matter in the brain and an improvement in neurocognitive function. The volume of white matter was found to increase due to the movement of water from extracellular to intracellular. The pathophysiology of this process was still unclear. In CKD, there are osmotic changes in the brain due to uremic accumulation and water retention. Under normal conditions, the brain can maintain a constant intracellular volume by adapting to osmotic pressure. However, in chronic inflammatory triggered by uremic toxins, there is cellular dysfunction and increased cellular permeability, leading to reduced intracellular volume in patients with CKD.[35] The finding of improved neurocognitive function in children with CKD who underwent transplantation compared with patients who had HD was in line with findings in adults. In a study by Posselt et al, who assessed neurocognitive function in adult patients with CKD who received transplants versus with adult patients receiving hemodialysis, it was found that neurocognitive function was better in several domains in adult patients who received kidney transplantation. This may also be due to improved post-transplant endocrine and exocrine function restoration, where potassium, phosphate, and calcium values become normal over time.[36]

Study Limitations

As the limitation of this study, currently, studies regarding the association between CKD with neurocognitive function in children are still limited, especially regarding the relationship between neurocognitive function and the therapeutic modality. The diversity of age ranges and the use of various neurocognitive examination methods can cause the results to be less specific, since every method to measure neurocognitive examination has different sensitivity and specificity. Each method might also measure different domain of neurocognitive with different method for different age range, and this might also affect the result. In the future, perhaps a similar systematic review study, which included more studies with more homogeneous age range samples and uniform assessment tools, can be done to draw more precise and detailed conclusions regarding neurocognitive function in children with CKD.

Conclusion

In children, CKD can cause neurocognitive function disorders through various complex and interconnected mechanisms, and affected by several factors, such as neurocognitive function disorders, including the education of parents, especially the mother's educational level, the therapeutic modalities used, the presence of depression, history of abnormal births, history of seizures, and hypertension. Treatment modality used might also affect the children's neurocognitive function. Children who underwent kidney transplant generally had better neurocognitive function compared to children who had other treatment modalities. In children with CKD, the generally impaired domains include attention, visual-spatial, visual working memory, verbal function, and executive function.

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Disclosure

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References

1. Mistry K. Chronic kidney disease. In: Kher KK, Schnaper HW, Grennbaum LA, editors. *Clinical Pediatric Nephrology.* 3rd ed. Taylor & Francis Group; 2017:601–626.
2. Claes DJ. Chronic kidney disease. In: Kliegman RM, St-Geme-III JW, Blum NJ, Shah SS, Tasker RC, Behrman KMWRE, editors. *Nelson Textbook of Pediatrics*. 21st ed. Canada: Elsevier; 2020.
3. Ardissino G, Dacco V, Testa S, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. *Pediatrics*. 2003;111(4):e382–e387. doi:10.1542/peds.111.4.e382
4. Noble R, Taal MW. Epidemiology and causes of chronic kidney disease. *Medicine*. 2019;47(9):562–566. doi:10.1016/j.mpmed.2019.06.010
5. Hilmanto D, Mawardi F, Lestari AS, Widiasta A. Disease-associated systemic complications in childhood nephrotic syndrome: a systematic review. *Int J Nephrol Renovasc Dis*. 2022;15:53. doi:10.2147/IJNRD.S351053
6. Chen K, Didsbury M, van Zwieten A, et al. Neurocognitive and educational outcomes in children and adolescents with CKD: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2018;13(3):387–397. doi:10.2215/CJN.09650917
7. Morales P, Loza R, Vasquez J, Baique P, Reyes M. Quality of life of children with chronic kidney disease undergoing renal replacement therapy. *J Kidney*. 2018;4(173):1220–2472.
8. Akranavičiūtė D, Ruževičius J. Quality of life and its components' measurement. *Eng Econ*. 2007;52:2.
9. Yapa HE, Purtell L, Chambers S, Bonner A. The relationship between chronic kidney disease, symptoms and health-related quality of life: a systematic review. *J Ren Care*. 2020;46(2):74–84. doi:10.1111/jorc.12303
10. Drew DA, Weiner DE. Cognitive impairment in chronic kidney disease: keep vascular disease in mind. *Kidney Int*. 2014;85(3):505–507. doi:10.1038/ki.2013.437
11. CASP Cross Sectional Checklist. Critical appraisal skills programme; 2018. Available from: https://www.unisa.edu.au/contentassets/72bf75606a2b4abcaf7f17404af374ad/2a-casp_cohort_tool.pdf. Accessed January 11, 2022.
12. Center for Evidence Based Management. Critical appraisal checklist for cross-sectional study. Available from: https://cebma.org. Accessed January 10, 2022.
13. Zyada F, Makar SH, Abdelrahman SM, Labana AH. Assessment of cognitive functions in children on regular hemodialysis and after renal transplantation. *Middle East Curr Psychiatry*. 2017;24(3):128–133. doi:10.1097/01.XME.0000516380.52486.97
14. Kogon AJ, Kim JY, Laney N, et al. Depression and neurocognitive dysfunction in pediatric and young adult chronic kidney disease. *Pediatr Nephrol*. 2019;34(9):1575–1582. doi:10.1007/s00467-019-04265-z
15. Molnar-Varga M, Novak M, Szabo AJ, et al. Neurocognitive functions of pediatric kidney transplant recipients. *Pediatr Nephrol*. 2016;31(9):1531–1538. doi:10.1007/s00467-016-3380-y
16. Johnson RJ, Warady BA. Long-term neurocognitive outcomes of patients with end-stage renal disease during infancy. *Pediatr Nephrol*. 2013;28(8):1283–1291. doi:10.1007/s00467-013-2458-z
17. Popel J, Joffe R, Acton BV, et al. Neurocognitive and functional outcomes at 5 years of age after renal transplant in early childhood. *Pediatr Nephrol*. 2019;34(5):889–895. doi:10.1007/s00467-018-4158-1
18. Hooper SR, Gerson AC, Johnson RJ, et al. Neurocognitive, social-behavioral, and adaptive functioning in preschool children with mild to moderate kidney disease. *J Dev Behav Pediatr JDBP*. 2016;37(3):231. doi:10.1097/DBP.0000000000000267
19. Ruebner RL, Laney N, Kim JY, et al. Neurocognitive dysfunction in children, adolescents, and young adults with CKD. *Am J Kidney Dis*. 2016;67(4):567–575. doi:10.1053/j.ajkd.2015.08.025
20. Mendley SR, Matheson MB, Shinnar S, et al. Duration of chronic kidney disease reduces attention and executive function in pediatric patients. *Kidney Int*. 2015;87(4):800–806. doi:10.1038/ki.2014.323
21. Berger I, Wu S, Masson P, et al. Cognition in chronic kidney disease: a systematic review and meta-analysis. *BMC Med*. 2016;14(1):1–10. doi:10.1186/s12916-016-0745-9
22. Harshman LA, Hooper SR. The brain in pediatric chronic kidney disease–the intersection of cognition, neuroimaging, and clinical biomarkers. *Pediatr Nephrol*. 2020;35(12):2221–2229. doi:10.1007/s00467-019-04417-1
23. Baune BT, Fuhr M, Air T, Hering C. Neuropsychological functioning in adolescents and young adults with major depressive disorder–a review. *Psychiatry Res*. 2014;218(3):261–271. doi:10.1016/j.psychres.2014.04.052
24. Gallibois CM, Jawa NA, Noone DG. Hypertension in pediatric patients with chronic kidney disease: management challenges. *Int J Nephrol Renovasc Dis*. 2017;10:205. doi:10.2147/IJNRD.S100891
25. Lande MB, Kupferman JC. Blood pressure and cognitive function in children and adolescents. *Hypertension*. 2019;73(3):532–540. doi:10.1161/HYPERTENSIONAHA.118.11686
26. Ostrovskaya MA, Rojas M, Kupferman JC, et al. Executive function and cerebrovascular reactivity in pediatric hypertension. *J Child Neurol*. 2015;30(5):543–546. doi:10.1177/0883073813494264
27. Mazumder MK, Paul R, Bhattacharya P, Borah A. Neurological sequel of chronic kidney disease: from diminished Acetylcholinesterase activity to mitochondrial dysfunctions, oxidative stress and inflammation in mice brain. *Sci Rep*. 2019;9(1):1–22. doi:10.1038/s41598-018-37935-3
28. Jabbari B, Vaziri ND. The nature, consequences, and management of neurological disorders in chronic kidney disease. *Hemodial Int*. 2018;22(2):150–160. doi:10.1111/hdi.12587
29. Olmos G, Muñoz-Félix JM, Mora I, et al. Impaired erythropoietin synthesis in chronic kidney disease is caused by alterations in extracellular matrix composition. *J Cell Mol Med*. 2018;22(1):302–314. doi:10.1111/jcmm.13319
30. Kaze FF, Nguefack S, Asong CM, et al. Birth weight and renal markers in children aged 5–10 years in Cameroon: a cross-sectional study. *BMC Nephrol*. 2020;21(1):1–9. doi:10.1186/s12882-020-02133-9
31. Carmody JB, Charlton JR. Short-term gestation, long-term risk: prematurity and chronic kidney disease. *Pediatrics*. 2013;131(6):1168–1179. doi:10.1542/peds.2013-0009

32. Sripada K, Bjuland KJ, Sølsnes AE, et al. Trajectories of brain development in school-age children born preterm with very low birth weight. *Sci Rep*. 2018;8(1):1–14. doi:10.1038/s41598-018-33530-8
33. Joseph RM, O'Shea TM, Allred EN, et al. Neurocognitive and academic outcomes at age 10 years of extremely preterm newborns. *Pediatrics*. 2016;137:4. doi:10.1542/peds.2015-4343
34. Madero M, Sarnak MJ. Does hemodialysis hurt the brain? In: *Seminars in Dialysis*. Wiley Online Library; 2011:266–268.
35. van Sandwijk MS, Ten BIJM, Caan MWA, et al. Cognitive improvement after kidney transplantation is associated with structural and functional changes on MRI. *Transplant Direct*. 2020;6:3. doi:10.1097/TXD.0000000000000976
36. Posselt J, Harbeck B, Rahvar A, Kropp P, Haas CS. Improved cognitive function after kidney transplantation compared to hemodialysis. *Ther Apher Dial*. 2022;25:931–938.