

Pediatric CKD: Integration of Magnetic Resonance Spectroscopy and Volumetric Analysis

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ABSTRACT

Background: Pediatric chronic kidney disease (CKD) is increasingly recognized as a systemic disorder with profound neurological consequences. Even in early stages, CKD can impair neurodevelopment through mechanisms including chronic uremia, anemia, hypertension, and metabolic acidosis. These systemic factors can disrupt neuronal metabolism, white matter maturation, and cortical growth, resulting in cognitive, behavioral, and motor deficits. Conventional neuroimaging often fails to detect subtle or early brain injury. Magnetic resonance spectroscopy (MRS) and volumetric MRI have emerged as advanced, noninvasive modalities capable of quantifying metabolic and structural brain alterations with high sensitivity, offering potential biomarkers for early detection and monitoring. This review synthesizes current evidence on the application of MRS and volumetric MRI in pediatric CKD, with emphasis on their ability to characterize metabolic derangements, detect structural brain volume changes, and provide integrated neuroimaging biomarkers. The objectives are to (1) outline the pathophysiological basis for CKD-related brain injury in children, (2) explain the technical principles and pediatric-specific considerations of MRS and volumetric MRI, (3) summarize existing literature on metabolic and structural alterations in this population, and (4) discuss how combined imaging approaches may improve prognostication and guide clinical interventions.

Conclusion: Studies using MRS in pediatric CKD consistently demonstrate altered metabolite ratios, including reduced N-acetylaspartate (NAA), elevated myo-inositol (ml), and variable choline (Cho) changes, reflecting neuronal loss/dysfunction, gliosis, and membrane turnover abnormalities. Volumetric MRI analyses reveal reductions in total brain volume, grey matter, and selected deep grey nuclei, alongside subtle white matter changes, some of which correlate with neurocognitive impairment. Integration of MRS and volumetric data enhances the understanding of disease burden, capturing both biochemical and morphological injury. These advanced MRI biomarkers hold promise for identifying subclinical brain injury, tracking progression, and evaluating the effects of therapeutic interventions. However, heterogeneity in study design, imaging protocols, and patient populations limits cross-study comparability. Standardization of acquisition, pediatric-specific normative databases, and longitudinal multicenter studies are essential to establish these modalities as routine tools in pediatric CKD care. Such efforts could enable earlier intervention, optimize neuroprotective strategies, and ultimately improve neurodevelopmental outcomes in this vulnerable population.

Keywords: *Pediatric CKD: Integration of Magnetic Resonance Spectroscopy and Volumetric Analysis*

INTRODUCTION

Pediatric chronic kidney disease (CKD) is a progressive condition with an estimated global prevalence of 75–100 cases per million children, and incidence rates continue to rise in both developed and developing countries [1]. While traditionally considered a disorder of renal filtration, CKD in children has profound systemic effects, with the central nervous system (CNS) increasingly recognized as a vulnerable target. Neurological manifestations can emerge early in the disease course, even before the onset of overt uremic encephalopathy. These range from subtle cognitive deficits to significant neurodevelopmental delay, often impacting academic performance, behavior, and quality of life [2].

Conventional structural MRI, although useful for detecting gross pathology such as infarcts or white matter lesions, lacks the sensitivity to identify early or diffuse microstructural brain injury associated with CKD [3]. Recent advances in neuroimaging, particularly magnetic resonance spectroscopy (MRS) and volumetric MRI, have enabled detailed assessment of brain metabolism and structure beyond the capabilities of standard imaging. MRS quantifies cerebral metabolites such as N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and myo-inositol (mI), which serve as biochemical markers of neuronal integrity, membrane turnover, and gliosis [4]. Volumetric MRI, using automated segmentation and voxel-based morphometry, provides objective quantification of brain regions, allowing for precise detection of cortical and subcortical volume changes [5].

Despite their potential, the application of these advanced MRI biomarkers in pediatric CKD remains underexplored. Existing studies are limited by small sample sizes, heterogeneous imaging protocols, and a lack of longitudinal follow-up. Moreover, most available research examines either metabolic or volumetric changes in isolation, rather than integrating these complementary modalities [6]. The aim of this review is to synthesize current evidence on the role of MRS and volumetric MRI in detecting and characterizing CKD-related brain injury in children. By examining the interplay between metabolic and structural alterations, we aim to highlight the potential for combined imaging biomarkers to improve early diagnosis, guide neuroprotective strategies, and monitor therapeutic outcomes in this high-risk population [7].

2. Pediatric CKD and Neurodevelopment

The pediatric brain undergoes rapid structural and functional maturation from infancy through adolescence, making it uniquely susceptible to systemic insults such as chronic kidney disease (CKD) [8]. CKD affects neurodevelopment via multiple interrelated mechanisms, including accumulation of uremic toxins, electrolyte disturbances, and persistent low-grade inflammation. These factors can impair neuronal differentiation, myelination, and synaptic pruning, potentially leading to long-term deficits in executive function, memory, and processing speed [9]. The timing of CKD onset is critical

— children diagnosed during key developmental windows often exhibit more severe neurocognitive outcomes than those with later-onset disease [10].

One major contributor to brain injury in pediatric CKD is chronic anemia, primarily due to reduced erythropoietin production and iron dysregulation [11]. Anemia leads to cerebral hypoxia, which in turn disrupts oligodendrocyte function and white matter development. Even mild reductions in hemoglobin have been associated with lower scores on standardized neuropsychological testing [12]. Similarly, hypertension, a frequent comorbidity in pediatric CKD, is linked to cerebrovascular remodeling, reduced cerebral perfusion, and microvascular injury. Over time, these hemodynamic stresses can accelerate brain atrophy and alter neural connectivity [13].

Metabolic acidosis, another common feature of CKD, alters the acid–base balance in the CNS, affecting enzyme activity and neurotransmitter synthesis [14]. Persistent acidosis has been implicated in neuronal apoptosis and reduced synaptic density, both of which may contribute to observed decreases in brain volume and cognitive performance. Furthermore, dysregulated calcium-phosphate metabolism in CKD can result in vascular calcifications, including intracranial vessels, potentially compromising nutrient delivery to developing neural tissues [15]. These systemic derangements are often present concurrently, creating a cumulative neurotoxic environment that can have irreversible consequences without early intervention.

Neurodevelopmental impairment in pediatric CKD is clinically heterogeneous, manifesting as deficits in attention, working memory, visuospatial processing, and psychomotor speed [16]. Early identification of at-risk children is challenging because subtle cognitive changes may precede overt neurological signs. This underscores the importance of advanced neuroimaging biomarkers, such as MRS and volumetric MRI, which can detect metabolic and structural abnormalities before clinical deterioration occurs. Integrating these modalities into routine evaluation could facilitate earlier intervention and potentially improve long-term neurodevelopmental trajectories [17].

3. Principles of Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is a noninvasive imaging technique that extends the capabilities of conventional MRI by providing biochemical information about brain tissue in vivo [18]. While standard MRI sequences generate images based on proton density and relaxation properties, MRS measures the resonant frequencies of specific metabolites, producing a spectrum rather than an anatomical image. The position and area under each spectral peak correspond to the chemical environment and concentration of metabolites within a predefined voxel. In pediatric neuroimaging, proton (^1H) MRS is most commonly used due to its high sensitivity, availability on clinical MRI scanners, and ability to detect key cerebral metabolites relevant to neuronal health and glial activity [19].

The primary metabolites assessed by MRS include N-acetylaspartate (NAA), creatine (Cr), choline-containing compounds (Cho), myo-inositol (mI), and the glutamate–glutamine complex (Glx) [20]. NAA is widely considered a marker of neuronal density and function; reductions in NAA often indicate neuronal loss or dysfunction. Cho reflects membrane synthesis and turnover, with elevations typically associated with demyelination or gliosis. Cr serves as a reference metabolite for energy metabolism due to its relatively stable concentration. mI is a glial marker, often elevated in gliosis and osmotic stress, while Glx is involved in excitatory neurotransmission and can be altered in metabolic encephalopathies. In pediatric CKD, disturbances in osmotic balance, uremic toxin accumulation, and cerebral perfusion can shift these metabolite levels, potentially offering early biomarkers of neural injury [21].

MRS data acquisition in children requires specific technical considerations to ensure reliability and reproducibility. Short echo times (TE) are preferred to capture metabolites with short T2 relaxation times, such as mI and Glx [22]. Sequence choice typically involves point-resolved spectroscopy (PRESS) or stimulated echo acquisition mode (STEAM), with PRESS being more common due to higher signal-to-noise ratio. Voxel placement is crucial and often targets regions vulnerable to CKD-related injury, such as the frontal white matter, parietal cortex, or deep grey matter nuclei. Pediatric imaging also requires strategies to minimize motion artifacts, including fast acquisition protocols, child-friendly preparation, and, when necessary, sedation [23]. These methodological refinements are essential for generating high-quality spectra suitable for quantitative analysis in research and clinical settings.

4. Brain Metabolic Alterations in Pediatric CKD

Multiple MRS studies have reported characteristic metabolic abnormalities in the brains of children with chronic kidney disease (CKD), even in the absence of overt neurological symptoms [24]. One of the most consistent findings is a reduction in N-acetylaspartate (NAA), which reflects compromised neuronal integrity or function. This decline has been observed in both cortical and subcortical regions, suggesting a diffuse rather than focal pattern of injury [25]. Such reductions may result from chronic hypoxia due to anemia, uremic toxin-induced mitochondrial dysfunction, or impaired axonal transport. In parallel, elevations in myo-inositol (mI) are frequently documented, often interpreted as evidence of gliosis and osmotic imbalance secondary to CKD-related metabolic derangements [26].

Alterations in choline (Cho) levels in pediatric CKD appear more variable across studies. Some investigations report elevated Cho, consistent with increased membrane turnover in demyelination or gliotic processes [27], while others observe no significant change compared to healthy controls. This heterogeneity may be due to differences in CKD stage, dialysis status, and region of interest selection. Similarly, creatine (Cr), often used as an internal reference in metabolite ratio calculations, can itself

be altered in CKD due to systemic creatine metabolism disturbances [28]. This complicates the interpretation of metabolite ratios and underscores the importance of absolute quantification when feasible.

The glutamate–glutamine complex (Glx) is another metabolite of interest, given its role in excitatory neurotransmission and ammonia detoxification. Elevated Glx has been observed in some pediatric CKD cohorts, potentially reflecting altered nitrogen metabolism and astrocytic dysfunction [29]. However, these findings are not universal and may depend on the degree of uremia and dialysis adequacy. Importantly, metabolic alterations on MRS have been shown to correlate with neurocognitive test scores in domains such as working memory, processing speed, and executive function, suggesting a direct link between biochemical disturbances and clinical outcomes [30].

Despite these insights, current literature on MRS in pediatric CKD remains limited by small sample sizes, cross-sectional designs, and methodological variability. Differences in voxel placement, echo time selection, and spectral processing can all influence measured metabolite concentrations [31]. Furthermore, most studies investigate single brain regions rather than whole-brain metabolic patterns, potentially missing widespread subclinical involvement. Longitudinal, multicenter studies with standardized acquisition protocols are needed to determine the trajectory of metabolic changes and their responsiveness to interventions such as dialysis optimization or kidney transplantation [32].

5. Principles of Volumetric MRI Analysis

Volumetric MRI analysis enables quantitative assessment of brain structure by measuring the size of global and regional brain compartments [33]. Unlike conventional MRI, which provides primarily qualitative assessments, volumetric approaches use high-resolution 3D T1-weighted sequences to create datasets suitable for automated segmentation and morphometric analysis. Techniques such as voxel-based morphometry (VBM), surface-based analysis, and atlas-based segmentation allow for objective comparison of brain volume between individuals or groups. These tools can detect subtle changes in grey and white matter that may be imperceptible to the naked eye, making them particularly useful for identifying early CKD-related neurostructural alterations [34].

One key application of volumetric MRI in pediatric populations is the ability to compare patient data to normative developmental trajectories [35]. The human brain undergoes region-specific growth patterns during childhood and adolescence — for example, grey matter volume peaks in late childhood before gradually declining, while white matter volume increases steadily into early adulthood. Pediatric CKD can disrupt these trajectories through metabolic injury, ischemia, and inflammation, leading to premature cortical thinning, delayed myelination, or regional atrophy. Volumetric metrics such as total intracranial volume (ICV), cortical thickness, and subcortical nucleus size can be

compared to age- and sex-matched controls to identify deviations suggestive of disease-related injury [36].

Pediatric volumetric studies face unique technical challenges. Motion artifacts are a common problem, particularly in younger children, and can degrade the accuracy of automated segmentation algorithms [37]. In addition, brain maturation introduces variability in tissue contrast and geometry that must be accounted for during analysis. To address these issues, many research protocols employ motion correction strategies, age-appropriate MRI templates, and advanced segmentation software such as FreeSurfer or FSL-FIRST. Another challenge is the lack of large-scale normative volumetric databases specifically for pediatric CKD, which limits the interpretation of subtle deviations from typical development [38]. Nevertheless, volumetric MRI remains a powerful tool for quantifying CKD-related brain changes, especially when combined with complementary metabolic data from MRS.

6. Brain Volume Changes in Pediatric CKD

Volumetric MRI studies in pediatric chronic kidney disease (CKD) consistently reveal evidence of brain atrophy, even in patients without overt neurological symptoms [39]. Reductions in total brain volume, as well as specific losses in grey and white matter compartments, have been documented across multiple cohorts [40]. These changes are often subtle but measurable with automated segmentation methods, suggesting that CKD induces diffuse neurostructural injury rather than isolated focal damage. The mechanisms are likely multifactorial, involving chronic metabolic stress, cerebrovascular compromise, and inflammatory processes that impair neural growth and maintenance [41].

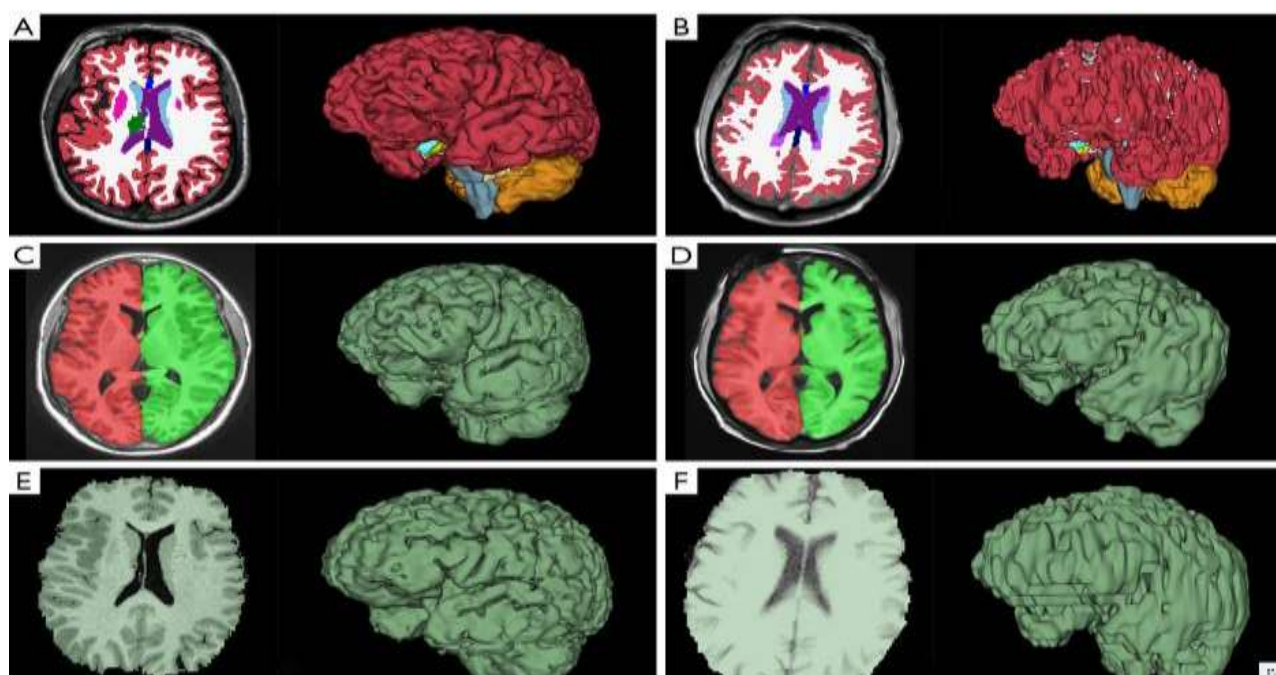


Figure 1: Examples of BV segmentations. (A) FreeSurfer BV using 3D T1 MRI. (B) FreeSurfer BV using 2D T1 MRI. (C) volBrain BV using 3D T1 MRI. (D) volBrain BV using 2D T1 MRI. (E) 3D Slicer BV using 3D T1 MRI. (F) 3D Slicer BV using 2D T1 MRI. The (A,C,E) segmentations and (B,D,F) segmentations are derived from two different subjects. BV, brain volume; MRI, magnetic resonance imaging [41].

Grey matter alterations are particularly notable in frontal and parietal cortices, regions critical for higher-order cognitive functions [42]. Cortical thinning in these areas may be related to the cumulative impact of uremic toxins, hypertension, and impaired cerebral autoregulation. Subcortical structures such as the hippocampus and basal ganglia have also been reported to exhibit reduced volumes in pediatric CKD [43]. These regions are metabolically demanding and highly vascularized, making them especially vulnerable to hypoperfusion and oxidative stress. Loss of hippocampal volume, in particular, correlates with deficits in memory and learning, while basal ganglia changes may contribute to psychomotor slowing and movement abnormalities [44].

White matter integrity is similarly affected, with volumetric reductions frequently observed in periventricular and deep white matter tracts [45]. These changes may result from delayed or disrupted myelination due to chronic metabolic acidosis, anemia, and electrolyte imbalances common in CKD. The impact of dialysis on white matter volume is complex; while some studies report partial recovery following transplantation, others note persistent deficits, suggesting that early damage may be irreversible without timely intervention [46]. Given that white matter supports the rapid transmission of neural signals, even modest volume loss in these tracts may significantly impair cognitive processing speed and executive function.

Despite these findings, volumetric MRI data in pediatric CKD remain limited by cross-sectional designs and small sample sizes [47]. There is a pressing need for longitudinal studies to track the progression of brain volume changes from early CKD through dialysis and transplantation. Establishing whether such changes stabilize, progress, or reverse with treatment would have important implications for monitoring and intervention. Integrating volumetric findings with metabolic data from MRS could further enhance understanding of the relationship between biochemical disturbances and structural injury, enabling the development of multimodal neuroimaging biomarkers [48].

7. Integration of MRS and Volumetric MRI Findings

The integration of metabolic and structural MRI biomarkers offers a more comprehensive assessment of brain injury in pediatric chronic kidney disease (CKD) than either modality alone [49]. While MRS detects biochemical disturbances such as reduced N-acetylaspartate (NAA) and elevated myo-inositol (mI), volumetric MRI quantifies macroscopic changes in grey and white matter volumes. Combining these techniques enables the identification of metabolic alterations that precede measurable atrophy, potentially allowing for earlier diagnosis and intervention [50]. For example, reduced NAA in the frontal cortex may signal early neuronal compromise before volumetric loss becomes apparent, while concurrent volume reduction in the same region could indicate chronic or irreversible injury [51].

Several studies have demonstrated correlations between MRS metabolite ratios and volumetric measurements in pediatric CKD populations [52]. For instance, children with elevated mI often exhibit reduced white matter volumes, suggesting that gliosis and osmotic dysregulation contribute to white matter loss. Similarly, hippocampal volume loss has been linked to reduced NAA levels, supporting the notion that metabolic impairment contributes directly to structural degeneration [53]. This multimodal approach not only improves the sensitivity of neuroimaging for detecting CKD-related brain injury but also facilitates a better understanding of the underlying pathophysiological mechanisms.

From a clinical perspective, integrating MRS and volumetric MRI could aid in stratifying patients by risk of neurocognitive decline and tailoring monitoring strategies [54]. Children showing both metabolic and structural abnormalities may require more frequent neuropsychological assessments, aggressive management of CKD-related risk factors, and earlier consideration of interventions such as transplantation. Furthermore, combined biomarkers could serve as surrogate endpoints in clinical trials evaluating neuroprotective therapies. However, implementing this approach in routine clinical practice requires standardized acquisition protocols, access to advanced post-processing tools, and normative pediatric datasets that account for developmental changes in metabolite concentrations and brain volumes [55].

8. Clinical Implications and Future Directions

The application of MRS and volumetric MRI in pediatric CKD has important implications for early diagnosis, risk stratification, and treatment monitoring [56]. Detecting subclinical brain injury before the onset of overt neurocognitive symptoms allows for timely interventions, such as optimizing dialysis adequacy, aggressive blood pressure control, and correction of anemia or metabolic acidosis. These interventions may mitigate further neurological decline and improve developmental outcomes. Moreover, identifying children with early metabolic abnormalities but preserved brain volume could help target neuroprotective therapies at a reversible stage of injury [57].

incidence rises with the progression of the CKD.

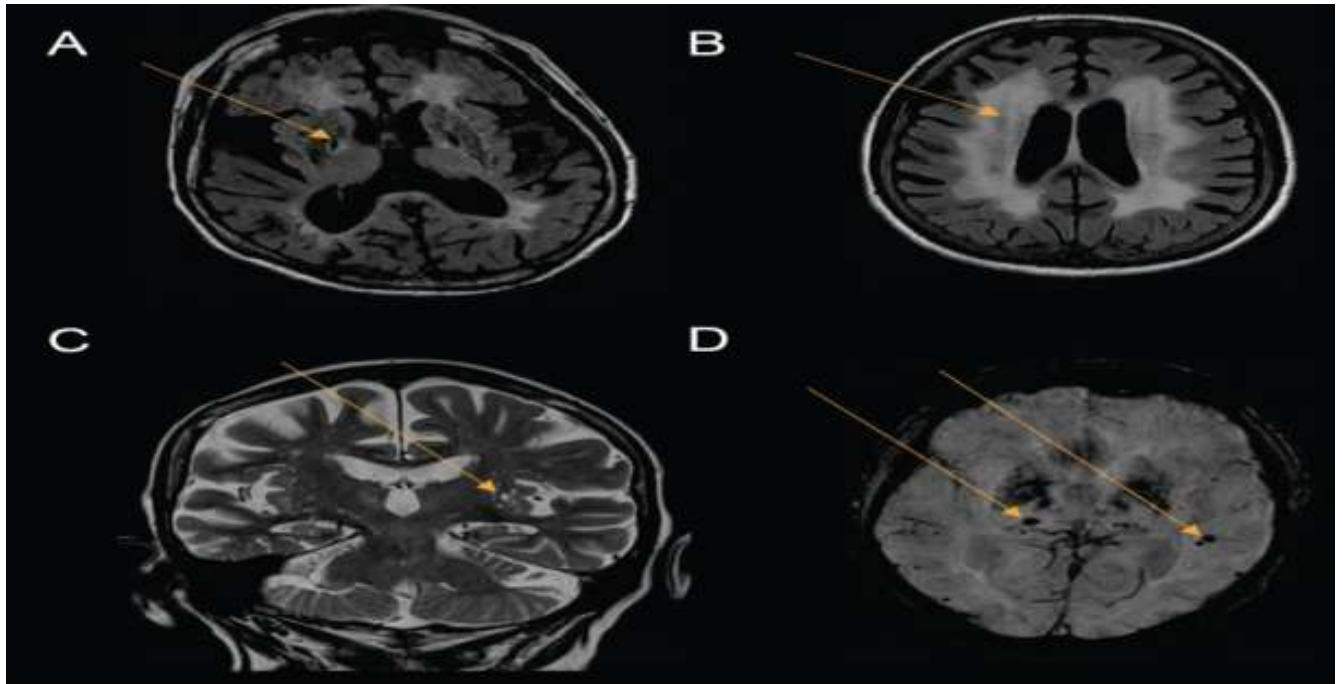


Figure 2: A) FLAIR T2WI MRI, chronic lacunar infarction (low intensity lesion with hyperintense rim of gliosis in the right lobe basal ganglia) B) FLAIR T2WI MRI, degeneration and gliosis of the white matter appear as extensive periventricular hyperintense lesions C) T2WI MRI, enlarged perivascular spaces D) SWI MRI, cerebral microbleeds - small areas of signal loss [57].

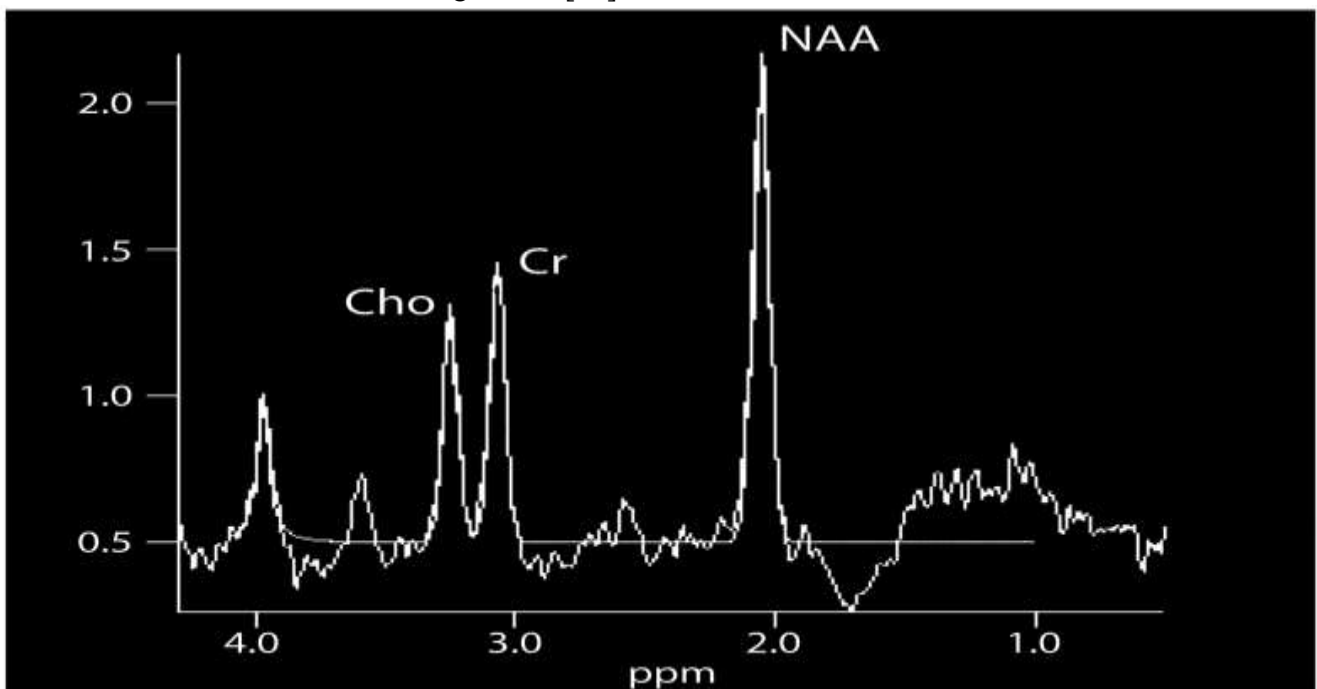


Figure 3 : MRS spectrum from an area of normal brain. Choline (Cho), creatine (Cr), and N-acetyl-aspartate (NAA) are the dominant peaks, with NAA higher than both Cho and Cr [57].

Incorporating advanced MRI biomarkers into routine pediatric CKD care also has potential value for longitudinal monitoring [58]. Serial MRS and volumetric MRI assessments can track the progression or stabilization of brain injury over time, providing objective data on the effectiveness of interventions such as transplantation. This is particularly relevant given the variability in neurocognitive outcomes

after kidney transplantation, where some children show improvement in brain structure and function while others exhibit persistent deficits. Longitudinal imaging could help identify factors influencing recovery and guide personalized treatment approaches [59].

From a research standpoint, multimodal neuroimaging offers an opportunity to refine our understanding of CKD-related neurobiology [60]. Standardizing acquisition protocols across centers would enable large-scale multicenter studies, increasing statistical power and generalizability. Developing pediatric-specific normative databases for MRS metabolites and volumetric parameters is essential for accurate interpretation. Furthermore, integrating imaging with serum biomarkers of inflammation, oxidative stress, and endothelial dysfunction could yield composite risk models for neurocognitive impairment, enhancing predictive accuracy [61].

Looking ahead, artificial intelligence (AI) and machine learning could play a transformative role in the analysis of MRS and volumetric MRI data [62]. Automated algorithms can detect subtle, spatially distributed changes in brain metabolism and structure that may be imperceptible to human observers. Predictive models trained on multimodal datasets could forecast neurocognitive outcomes and identify optimal intervention windows. However, these advances must be accompanied by robust ethical safeguards, data privacy protections, and strategies to ensure equitable access to advanced imaging for all pediatric CKD patients, including those in resource-limited settings [63].

9. Conclusion

Pediatric chronic kidney disease exerts a profound and multifactorial impact on brain development, with metabolic and structural changes detectable long before clinical symptoms emerge. Magnetic resonance spectroscopy (MRS) and volumetric MRI offer complementary, noninvasive biomarkers capable of capturing these early alterations. MRS provides insights into neuronal health, glial activity, and osmotic balance, while volumetric MRI quantifies cortical and subcortical atrophy and deviations from normal developmental trajectories. Integrating these modalities enhances diagnostic sensitivity, improves risk stratification, and supports targeted intervention planning. The evidence to date underscores the urgent need for standardized imaging protocols, multicenter collaborations, and pediatric-specific normative datasets. Such advances will be essential to transition these tools from research applications to routine clinical use, ultimately improving neurodevelopmental outcomes and quality of life for children living with CKD.

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