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RESEARCH ARTICLE

RELIABILITY OF MAGNETIC RESONANCE ENTEROGRAPHYAND DIFFUSION WEIGHTED IMAGINGIN ASSESSMENT OF ACTIVE CHRONSDISEASE IN CHILDREN

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ABSTRACT

Background: Chrons is a relapsing remitting disease that affects children and demands a reliable diagnostic tool to detect active episode with minimum hazards. **Objectives**: i- to assess the reliability of MR enterography, quantitative and qualitative DWI measurements done by radiologists of different experiences in assessment of disease activity in children, ii to explore if diffusion weighted imaging (DWI) can substitute contrast enhanced images. **Methods:** Post contrast MR Enterography with DWI of 32 patients suspected to have active chron's disease were retrospectively evaluated by 3 radiologists with different years of experience. Magnetic resonance score ≥7 was used as reference of activity. **Results:** 21 patients had active lesions. There was almost perfect inter-reader agreement regarding graded DWI hyperintensity (ICC)= 0.93. There was significant moderate correlation between graded DWI hyperintensity and MaRIA (r = 0.64),mMaRIA (r=0.65). DWI hyperintensity had sensitivity of 100%, specificity of 95.5% in detecting active disease. Mean ADC for active lesions was 1.4 ± 0.2 × 10-3 mm2 /s. A proposed cut-off 1.67 x10-3 mm2/sec had sensitivity of 100%, specificity 62.5. There was significant moderate inverse correlation between ADC values and MaRIA, mMaRIA, mural thickness and wall edema, while there was no significant correlation between ADC and ulcers or relative contrast enhancement. The 3 readers did not find significant difference in lesion visibility between (DWI + ADC) and (post contrast images). **Conclusions:** MRE with DWI is a reliable tool that accurately assessed activity of chron's disease, regardless the experience of readers. DWI is comparable to post contrast images in detection of active disease.

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INTRODUCTION

Pediatric patients with inflammatory bowel disease (IBD) commonly need repetitive imaging to assess disease activity and complications (Morani, 2015). Magnetic resonance enterography (MRE) is now rapidly replacing Computed tomography enterography (CTE) in many centers. Its main advantage over CTE is lack of radiation exposure, superior soft tissue contrast and ability to evaluate enteric peristalsis with Cine sequences (AlSabban, 2017). However, it is more liable to motion artefacts and compliance problems especially in young children. In patients diagnosed with the inflammatory bowel disease prior to 17 years of age; the riskof developing malignant neoplasms due toaccumulated radiation doses, is twice ashigh as in adults. This risk is influenced by the early onset and number of exacerbations thatrequires repeated testing. Another factor is the higher rate of cell division in young patients (Sanka, 2012; Markova, 2010; Giles, 2012; Chatu, 2012 and Giles, 2013). As the nature of the disease implies repeated examinations that are reported by different sets of radiologists and even in different institutions, the needof reliablescoring index that is less liable to personal variations became a must. Another issue is raised recently regarding the accumulation of gadolinium compounds in the basal ganglia (Stojanov, 2016), which in turn necessitates new techniques that doesn't require contrast injection. Diffusion-weighted imaging (DWI) is one of the magnetic resonance imaging (MRI) sequences providing qualitative as well as quantitative information that reflects mobility of water molecules and tissue cellularity (AlSabban, 2017). Over the past decade, various extracranial applications of DWI have been explored, furthermore it was reported that it could detect

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abnormalities even before signal or morphological changes become apparent on other pulse sequences. Different ADC cutoff values have been descried to detect disease activity, yet it seems to be little bit time consuming and liable to bias. Another more convenient method is visual qualitative assessment of diffusion restriction, again this method is liable to personal variations related to different degrees of experience. The purpose of this article is:i-to assess the reliability of MR enterography, quantitative and qualitative DWI measurements done by radiologists of different experiences in assessment of disease activity in children, ii to explore if DWI can substitute contrast enhanced images.

PATIENTS AND METHODS

This study was carried on after approval from the local ethical committee of Dar Al-Shifa Hospital, the need for informed consent was waived owing to the retrospective nature of the study. However, informed consents for MRI contrast intake were available for all patients.

Study population: During the period from January 2015 till July 2018, (32) patients suspected to have active inflammatory bowel disease were enrolled in this retrospective study. The criteria of enrollment included: Age below 18 Y with previous histopathological proof of having intestinal (either small intestinal or colonic) chronic inflammatory bowel disease. The criteria of exclusion were: intolerance or contraindication to undergo MRE; creatinine clearance < 30.

MR imaging: Magnetic resonance enterography (MRE) was performed using 3T (Magnetom Skyra siemens) system as per usual clinical practice. Patient preparation: patients had to fast not less than four hours prior to examination. No bowel cleansing agents were admitted to patients. Patients received oral contrast 1200 ml of 2.5% mannitol solution over 60 minutes to distend the small bowel prior to MRI examination. No intravenous spasmolytic agent, nor water rectal enema were given.

Image acquisition: Patients were placed prone in the magnet and an18 -channel phased array body coil was used. First a HASTE localizer was acquired, followed by; breath hold axial/ coronal T2 HASTE (FOV: 350 mm, No. of slices: 35, Slice thickness: 5/4, Repetition time: 1300/1200ms, Echo time: 92ms, image matrix: 320, averages:1, Flip angle: 180/176), True FISP fat sat axial and coronal (FOV: 350 mm, No. of slices: 50/65, Slice thickness: 3, Repetition time: 448,62 ms, Echo time: 2.3ms, image matrix:256, averages:1, Flip angle: 60), T1 VIBE Dixon FLASH fat sat axial and coronal (FOV: 350 mm, No. of slices: 35, Slice thickness: 3, Repetition time: 6.68ms, Echo time1: 2.39ms, Echo time2: 4.77ms, image matrix: 320/352, averages: 1, Flip angle: 10). Diffusion weighted images were taken prior to injection of IV contrast. Free breathing axial diffusion MRI was acquired utilizing an echo-planar imaging (EPI) sequence. A spectrally adiabatic inversion recovery (SPAIR) was applied for fat-suppression (FOV:380 mm, No. of slices: 30, Slice thickness: 6mm, Repetition time: 3200ms, Echo time:53 ms, concatenations: 2, base resolution: 134, phase resolution: 100%). Four b values (0, 50,400, and 800) were obtained. Finally post contrast T1 VIBE Dixon axial and coronal 45 and 70sec after injection of 0.1 mmol/kg of Dotarem (gadoterate meglumine, Guerbet LLC, USA) at flow rate of 3mm/sec using automatic injector. The approximate acquisition time of the examination was 30 minutes.

Image interpretation: Images were interpreted by3radiologists with10, 5 and 2 years of experience in pediatric abdominal imaging, they were unaware to clinical symptoms, Lab or colonoscopy results. Analysis was done using a dedicated post-processing software (Care stream packs). Three sets of images; (T2 with fat suppression axial and coronal image), DWI and ADC map) and (post contrast axial and coronal images) were evaluated by the 3 radiologists in a period of 4 weeks apart. The small bowel was divided into three segments; jejunum, proximal ileumand terminal ileum (defined as 20 cm of the distal end of the ileum nearest to the ileo-cecal valve). The colon was divided into fivesegments; ascending colon (including the cecum), transverse colon, descending colon, sigmoid colon, and rectum. First, the 3 readers had to score the visibility of the lesion in each set of images (0= no lesion detected, 1= there is probably a lesion, 2=there is a definite lesion). Then a standardized data sheet was used to record inflammatory changes in each bowel segment that included the following characters: a) wall thickness (> 3mm in small bowel,> 6mm in the colon, b) mucosal ulcers (defined as deep depressions in the mucosal surface of the thickened loop), c) presence of mural edema (high SI on T2-weighted sequences of the bowel wall relative to the signal of the nearby psoas muscle), d) enlarged regional mesenteric lymph nodes, e) presence of fistula or abscess, f) free intra-peritoneal fluid, g) presence of fibro-fatty infiltration, h) relative contrast enhancement (RCE); wall signal intensity (WSI) was measured at the same point before and after contrast enhancement, then RCE was calculated using the formula:

RCE = [(WSI post-gadolinium - WSI pre-gadolinium)/ (WSI pre-gadolinium)] x100 x (SD noise pre-gadolinium/SD noise post-gadolinium). (Buisson, 2013 and Choi, 2016). Then the segment with the most severe lesions was used to calculate the MaRIA score [=1.5 x wall thickening (mm) + 0.02 x RCE (enhancement) +5 x edema + 10 x ulcers].[10, 11] Modified mMaRIA was calculated excluding the data of RCE. The effects of distension, susceptibility artefact and motion were also assessed. Restricted diffusion was defined as a high signal intensity in DWI in 800 b-value images combined with low signal intensity and low values in apparent diffusion coefficient (ADC) images. Graded qualitative DWI assessment of small and large bowel was done following Oto et al (Oto, 2009), 0 equals definitely absent (imperceptible wall, both in signal and in thickness), 1 equals probably absent (signal intensity and thickness are similar to the surrounding bowel segments), 2 equals probably present (normal wall thickness, but signal intensity is bright on DWI and dark on ADC map), and 3 equals definitely present (bowel wall thickness > 3mm, and bright signal intensity on DWI and dark on ADC map). Scores 0 and 1 were categorized as normal bowel wall, while scores 2 and 3 were categorized as bowel wall active inflammatory disease on DWI. Quantitative analysis used measurement of apparent diffusion coefficient (ADC) in the axial plane by a ROI placed on the area displaying the most restricted diffusion and showing the maximum mural thickening. The mean of the three ADC values taken by the 3 readers was accepted as the ADC value of the most affected segment and was used for statistical analysis.

Lab tests: Complete blood picture, C reactive protein, serum creatinine (for patients who are: diabetics, history of organ transplant or who are taking immunosuppressive therapy).

Statistical analysis: Quantitative variables are given as means and standard deviation (SD) or as medians in the case of an abnormal distribution. Proportions are expressed as percentages and 95% confident intervals (CIs). Differences in quantitative measures were tested by Student's test or Kruskal Wallis' test if the conditions of Student's test were not met. A threshold was determined by calculating receiver operating characteristic (ROC) curves. An AUC of 0.6–0.7 was considered poor, and 0.9–1 as excellent. The correlations between MaRIA, modified MaRIA score and ADC values obtained were calculated by Pearson rank correlation test. MRIA score ≥ 7 was considered as indicator of active disease. The correlation between ADC values and other parametric variables was calculated using Pearson rank correlation test. Spearman correlation test is used when correlation is calculated with non-parametric variables. Correlation r values < 0.3 were considered as weak to low correlation, 0.3-0.49 as low to moderate correlation, 0.5-0.69 as moderate correlation and ≥ 0.7 as strong correlation. Inter-observer agreement was assessed using variance component analysis with calculation of average intra-class correlation coefficient (ICC). Values less than 0.5 (poor), between 0.5 and 0.75 (moderate), between 0.75 and 0.9 (good), and greater than 0.90 (excellent). A ***P*** value of 0.05 was considered significant. Calculations were done using SPSS 20.

RESULTS

Patient population; this study included 32 cases with 265 segments, seventeen were males, mean age (14.4 ± 1.7). The examination was well tolerated by all patients.

Magnetic resonance enterography (MRE) Findings: MRE examination was considered adequate for diagnosis in all patients by the 3 radiologists with good bowel distension. High image quality was reported in all MRE examinations. There was no difference in the choice of the segment that showed severe involvement in each patient among the three observers. Active lesions were reported in 21 patients (66%) defined as a MaRIA score ≥ 7. The most affected segment was located at the terminal ileum 18 patients (72%), proximal ileum in 3 patients (12 %), descending colon in 2 patients (8%), jejunum in one patient (4%), and rectum in one patient (4%). There was perfect inter-observer agreement between the 3 readers as regard mural thickening and edema (ICC= 1), good inter-observer agreement regard presence of ulcers (ICC=0.62m p=0.002), moderate inter-observer agreement regarding RCE, MaRIA and mMaRIA (ICC= 0.81, 0.78 and 0.75, P=0.004, 0.000 and 0.000 respectively). The rest of morphological features showed perfect inter-observer agreement. Fibrofatty infiltration was detected in 21 cases (all cases with active disease), 7 cases had abscess, 2 cases had fistulae, one patient had stricture, mesenteric lymph nodes were detected in 17 patients and ascitesin 10 patients. MRE Findings are listed in Table 1 and examples are given in Figures 1- 4.

DWI hyperintensity (qualitative criteria): Almost all cases with inactive disease showed grade 1 by the 3 readers, apart from one case thatwas reported as grade 2 hyperintensityby 2 readers. All cases with active disease (defined as MRIA score ≥ 7) showed either grade 2 or 3 by the 3 readers with average interclass coefficient (ICC)= 0.93.

Table 1. Morphological features (not included in MaRIA score) detected in MRE

Findings	Number of cases
Fibrofatty infiltration	21
Abscess	7
fistula	2
stricture	1
Mesenteric lymphadenopathy	17
ascites	10

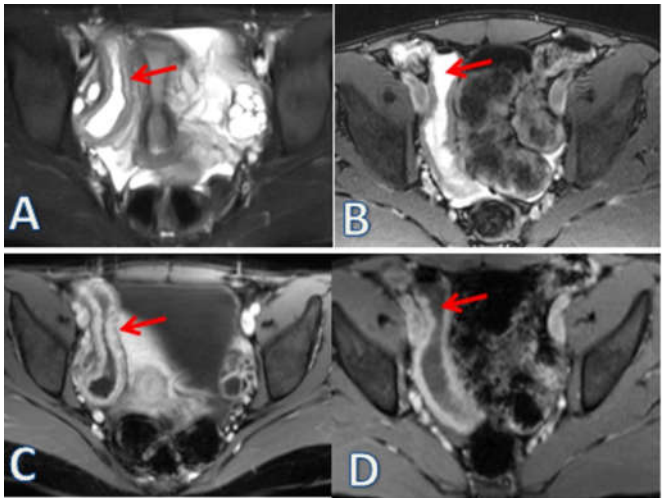

Fig. 1. Different components of MaRIA score; A: axial T2 WI with fat suppression showing mural thickening and edema of the terminal ileum associated with mild pelvic free fluid. B: axial T2 with fat suppression showed superficial ulcers at terminal ileum. C: axial post contrast image showed significant mucosal enhancement of the terminal ileum. D: axial post contrast showed superficial ulcers at terminal ileum.

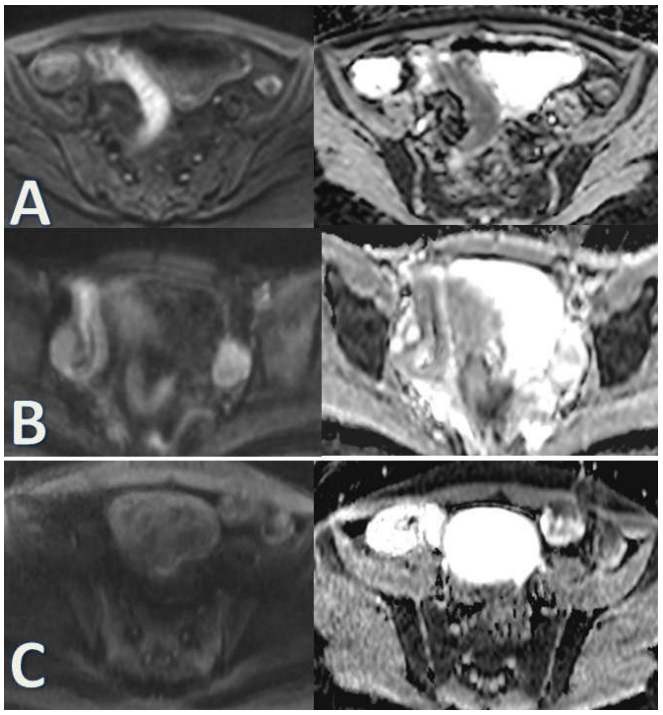

Fig. 2. DWI grading; A&B :grade 3 (definitely present) mural thickness more than 3 mm with bright SI in DWI, dark SI in ADC of the terminal ileum. C: grade 0 (definitely absent) imperceptible wall and SI of the terminal ileum

There was significant moderate correlation between graded DWI hyperintensity and MaRIA (r = 0.64, P= 0.00), mMaRIA (r=0.65, P=0.00). DWI hyperintensity had sensitivity of 100% (CI: 85.2-100), specificity of 95.5% (CI: 77.2-99.9), accuracy

of 97.7% (CI:87.7-99.9), negative predictive value of 100% and positive predictive value of 95.5% (CI:75.6-99.3) in detecting active disease.

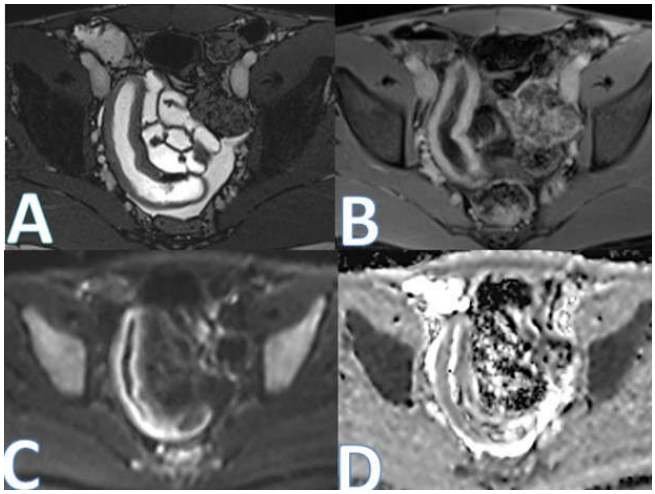

Fig. 3. A case of active chron's disease. A: axial T2 WI with fat suppresion showed mural thickening and edema of the terminal ilem. B: axial post contrast showing significant enhancement. C & D: axial DWI and ADC showed restricted diffusion (grade 3)

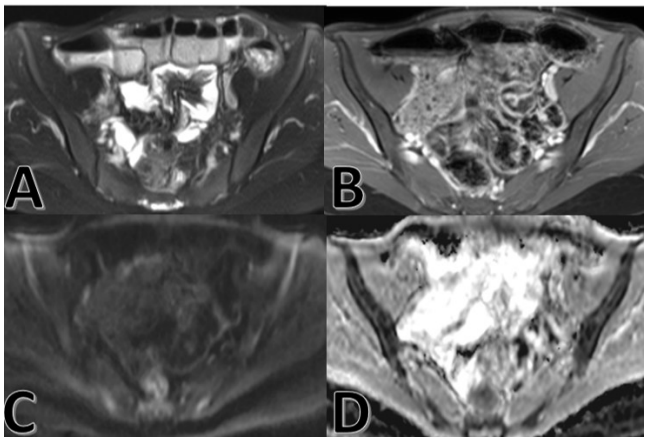

Fig. 4. A case of in-active chron's disease. A: axial T2 with fat suppression showed normal mural thickness of the terminal ileum, no edema or ulcers. B: axial post contrast showed no significant enhancement. C & D: axial DWI and ADC showed grade 0 (definitely no lesion)

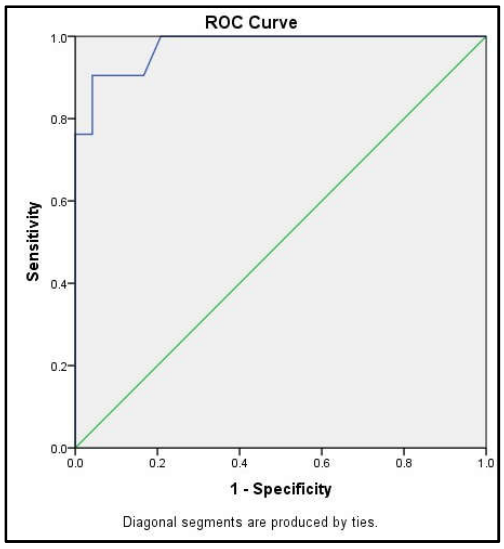

Fig. 5. ROC curve showing sensitivity and specificity when using ADC value of 1.67 x10-3mm2/sec for discrimination between active and non-active disease

ADC values (quantitative criteria): The mean ADC for bowel segments with active disease was $1.4 \pm 0.2 \times 10\text{-}3$ mm2 /s compared with $2 \pm 0.6 \times 10\text{-}3$ mm2/s for segments without active disease, a difference that was statistically significant ($P < 0.01$, Student's t-test). There was significant moderate inverse correlation between (ADC values) and MRIA, mMaRIA, wall thickness, wall edema (r=-0.59p =0.00, r=-0.67p=0.00, r=-0.53 p=0.00, r=-0.64 p=0.00). There was no significant correlation between ADC values and ulcers or relative contrast enhancement (r=-0.15p=0.48, r=-0.18 p=0.09). Area under the Receiver-operating characteristics (ROC) curve was 0.98 (95%CI: 0.94-1) as shown in figure 5. Using ROC curve, we determined a threshold of 1.67 x10-3mm2/sec for discrimination between active and non-active disease, with sensitivity of 100%, specificity of 62.5%, accuracy of 81.4% (CI:65.9-91.4), negative predictive value of 100% and positive predictive value of 72.4% (CI:60.3-81.9).
There was no significant difference between visibility of lesions recorded by the 3 readers in T2, DWI +ADC and post contrast images.

DISCUSSION

Several MRI derived score systems were established and were correlated with clinical, lab, endoscopic and histopathological grading systems. Magnetic resonance index of activity (MaRIA) is a widely used score system that has been strongly correlated with the Crohn's disease endoscopic index of severity (CDEIS) (Ohtsuka, 2016; Ord´asI,, 2014; Van Assche, 2013 and Rimola, 2011). In the current study we used MaRIA and its modified form (mMaRIA) as indicator of activity of chrons disease. We found moderate inter-observer agreement among 3 readers regarding MaRIA and mMaRIA (ICC = 0.78 and 0.75) which reflected high reliability. Tielbeeket al [17] demonstrated moderate inter-observer agreement (ICC=0.74) between 4 readers with different clinical experience. Rimolaet al. (Rimola, 2017) and Kim et al. (Kim, 2017), reported similar results. When it comes to individual components of MaRIA; mural thickening and edema got the highest agreement while ulcers got the lowest. We believe that this could be attributed to absence of standard way to assess the presence of ulcer which really needs careful inspection while other parameters are easily measured or compared to nearby structures. Another study reported that the best inter-rater agreement was for decreased motility and wall DWI hyperintensity (Church, 2017). Coimbra et al stated that MRE provides images with high quality and reproducibility, even in a global multicenter setting for lesion detection in chrons disease (Coimbra, 2016). Another study reported good interobserver agreement (mean difference between MR enterography scores was -0.03; limits of agreement -2.8 to 2.7) (Campari, 2017).

We found that MaRIA and mMaRIA score had significant moderate inverse correlation to ADC values and significant moderate correlation to DWI hyperintensity. This copes with Hordonneau *et al* (Hordonneau, 2014), who used MaRIA score >7 as marker of activity and found that subjective presence of abnormal DWI had high sensitivity for segmental disease activity in adult population. Other studies using CDAI (Lim, 2015) and high fecal calprotectin (Pendse, 2017) as indices of activity found positive correlation with DWI. The latter study reported that abnormal DWI signal had 83% sensitivity, 52% specificity for detection active disease (Pendse, 2017). A meta-analysis study stated that the most important signs of inflammation were wall thickness and wall T2-hyperintensity

(mural edema). (Church, 2015). We found that these 2 features had significant moderate inverse correlation with ADC values and significant moderate correlation with DWI hyperintensity. On the controversy, Ream et al. (Ream, 2013), found that there was no significant correlation between ADC values and mural edema, length of disease involvement or mesenteric fibrofatty proliferation. While in the same study (Ream, 2013), they reported significant negative correlation between ADC values and bowel wall thickening, degree of arterial and delayed enhancement as well as amount of mesenteric inflammatory changes and presence of a stricture. We proposed a cut off value of 1.67 x10-3mm2/sec for discrimination between active and non-active disease, with sensitivity of 100%, specificity of 62.5%, accuracy of 81.4%. Shenoy-Bhangle whofound that the mean ADC for bowel segments with active disease was $1.56 \pm 0.7 \times 10\text{-}3$ mm2/sec (Shenoy-Bhangle, 2016). However, they suggested a high threshold value of $2.0 \times 10\text{-}3$ mm2/sec, with lower accuracy (64.1%) but higher sensitivity (78.8%) for detecting active disease compared with standard MR enterography (69.2% and 54.6%, respectively). While other researchers reported lower threshold value of 1.17x10 -3mm2/s with 100% sensitivity and 88% specificity for detection of active disease (Li, 2015). However the latter study included both children and adults among their study population.

Diffusion-weighted imaging was reported to be competitive or even superior to contrast-enhanced magnetic resonance imaging (MRI) for detection of bowel inflammation by several researchers (Oto, 2009; Oto, 2011; Kiryu, 2009 Neubauer, 2013 ; Oussalah, 2010 and Farah Khachab, 2018). This cope with our results as there was no significant difference between visibility of lesions recorded by the 3 readers in T2, DWI +ADC and post contrast images. Another recent study (Seo, 2016), declared that DWI is not inferior to contrast material-enhanced sequences for the evaluation of inflammation in Crohn's disease, except for the diagnosis of penetrating lesions. In their study DWI and contrast enhanced MRE identified bowel inflammation with agreement of 91.8% (157 of 171 segments). Sohn *et al* (Sohn, 2014), reported nearly similar results in pediatric population as DWI had lesion detection rate of 90.2% in lesion detection while atrial, portal and delayed phased of contrast enhanced had MRE had 92.7, 95.1 and 95.1% respectively. Another study reported that DWI combined with T2 WI had diagnostic performances equal or superior to post contrast-enhanced sequences for the detection of active inflammatory lesions and associated extraluminal complications of chrons disease (Neubauer, 2013). This study had a few limitations. First, we used MRE derived score system (MaRIA) as index of activity which could subjected to more bias. Second, we used the most affected segment for analysis, although this does not represent the global activity of chrons disease, but we thought that treatment decision would be changed according to the most severe lesion. Third, we assessed DWI and measured ADC of small and large bowel loops, but we did not categorize them in different groups. Fourth; we did not use motility sequences and assess inter-reader agreement. Lastly; we had small number of cases.

Conclusions

MRE with DWI is a reliable tool that accurately assessed activity of chron's disease, regardless the experience of readers. DWI is comparable to post contrast images in detection of active disease.

- Avoiding the hazards of radiation and minimizing IV contrast use in imaging of children and young adults is a priority.
- MRE utilizing different sequences and specified scores is reliable and reproducible diagnostic tool to assess activity of chrons disease
- Quantitative and qualitative DWI measurements are good alternatives to contrast enhanced images.

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REFERENCES

AlSabban, Z., Church, P., Moineddin, R., Navarro, O.M., Greer, M.L., Walters, T., Chavhan, G.B. 2017. Accuracy and interobserver agreement of diffusion-weighted imaging in pediatric in*fl*ammatory bowel disease. Clinical Imaging.,41:14–22

Buisson A, Joubert A, Montoriol PF, *et al.* 2013. Diffusion - weighted magnetic resonance imaging for detecting and assessing ileal inflammation in Crohn's disea se. *Aliment Pharmacol Ther.,* 37(5):537-45.

Campari, A., Napolitano, M., Zuin, G., Maestri, L., Di Leo, G., Sardanelli, F. 2017. Colonic inflammation in pediatric inflammatory bowel disease: detection with magnetic resonance enterography. *Pediatr Radiol.,* 47(7):850-859.

Chatu S, Subramanian V, Pollok RCG. 2012. Meta-analysis: diagnostic medical radiation exposure in inflammatory bowel disease. *Aliment Pharmacol Ther.,* 35: 529–539.

Choi SH, Kim KW, Lee JY, Kim KJ, Park SH. 2016. Diffusion-weighted Magnetic Resonance Enterography for Evaluating Bowel Inflammation in Crohn's Disease: A Systematic Review and Meta-analysis. Inflamm Bowel Dis.,22(3):669-79.

Church PC, Greer MC, Cytter-Kuint R, et al. 2017. Magnetic resonance enterography has good inter-rater agreement and diagnostic accuracy for detecting inflammation in pediatric Crohn disease .*Pediatr Radiol.,* 47(5):565-575.

Church, P.C., Turner, D., Feldman, B.M., et al. 2015. Systematic review with meta-analysis: magnetic resonance enterography signs for the detection of inflammation and intestinal damage in Crohn's disease. Aliment PharmacolTher., 41:153-166.

Coimbra, A.J., Rimola, J., O'Byrne, S., *et al*. 2016. Magnetic resonance enterography is feasible and reliable in multicenter clinical trials in patients with Crohn's disease, and may help select subjects with active inflammation. *Aliment Pharmacol Ther.,* 43:61-72.

Farah Khachab, Anderson Loundou, Anderson Loundou, et al. 2018. Can diffusion weighting replace gadolinium enhancement in magnetic resonance enterography for inflammatory bowel disease in children?. *Pediatric Radiology.*, 48: 132-1440.

Giles E, Barclay AR, Chippington S, Wilson DC. 2013. Systematic review: MRI enterography for assessment of small bowel involvement in paediatric Crohn's disease. *Aliment Pharmacol Ther.,* 37: 1121–1131.

Giles E, Hanci O, McLean A, *et al.* 2012. Optimal Assessment of Paediatric IBD With MRI and Barium Follow-through. *J Pediatr Gastroenterol Nutr.,* 54 (6): 758–762.

Hordonneau, C., Buisson, A., Scanzi, J., *et al.* 2014. Diffusion weighted magnetic resonance imaging in ileocolonic Crohn's disease: validation of quantitative index of activity. *Am J Gastroenterol.,* 109(1):89–98

Kim JS, Jang HY, Park SH, *et al.* 2017. MR Enterography Assessment of Bowel Inflammation Severity in Crohn Disease Using the MR Index of Activity Score: Modifying Roles of DWI and Effects of Contrast Phases. *AJR Am J Roentgenol.*, 208: 1022–1029.

Kiryu, S., Dodanuki, K., Takao, H., *et al.* 2009. Free-breathing diffusion weighted imaging for the assessment of inflammatory activity in Crohn's disease. *J Magn Reson Imaging.,* 29:880–886.

Li, X., Sun, C., Mao, R., *et al*. 2015. Assessment of Activity of Crohn Disease by Diffusion-Weighted Magnetic Resonance Imaging.Medicine (Baltimore)., 94(43): e1819.

Markova, I., Kluchova, K., Zboril, R., Mashlan, M., Herman, M. 2010. Small bowel imaging – still a radiologic approach?. Biomed Pap Med Fac Univ Palacky Olomouc *Czech Repub.,*154:123–132.

Morani AC, Elsayes KM, Liu PS, *et al.* 2013. Abdominal applications of diffusion-weighted magnetic resonance imaging: Where do we stand? *World J Radiol.,* 28;5(3):68-80.

Morani, A.C., Smith, E.A., Ganeshan, D., Dillman, J.R. 2015. Diffusion-weighted MRI in pediatric inflammatory bowel disease. *AJR Am J Roentgenol.,* 204(6):1269-77.

Neubauer, H., Pabst, T., Dick, A., et al. 2013. Small-bowel MRI in children and young adults with Crohn disease: retrospective head-to-head comparison of contrast-enhanced and diffusion-weighted *MRI. Pediatr Radiol.,* 43:103–114.

Neubauer, H., Pabst, T., Dick, A., Machann, W., *et al.* 2013. Small-bowel MRI in children and young adults with Crohn disease: retrospective head-to-head comparison of contrast-enhanced and diffusion-weighted MRI. *Pediatr Radiol.,* 43: 103–14.

Ohtsuka K, Takenaka K, Kitazume Y, *et al.* 2016. Magnetic resonance enterography for the evaluation of the deep small intestine in Crohn's disease. *Intest Res.,* 14(2):120-126

Ord´asI, Rimola J, Rodr´ıguez S *et al.* 2014. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. *Gastroenterology.,*146 (2): 374-382.

Oto A, Zhu F, Kulkarni K, et al. 2009. Evaluation of diffusion-weighted MR imaging for detection of bowel inflammation in patients with Crohn's disease. *Acad Radiol.,* 9;16:597–603.

Oto, A., Kayhan, A., Williams, J.T., *et al.* 2011. Active Crohn's disease in the small bowel: evaluation by diffusion weighted imaging and quantitative dynamic contrast enhanced MR imaging. *J Magn Reason Imaging.*, 33:615–624.

Oussalah, A., Laurent, V., Bruot, O., *et al*. 2010. Diffusion-weighted magnetic resonance without bowel preparation for detecting colonic inflammation in inflammatory bowel disease. Gut., 59:1056-1065.

Pendse,´D.A., Makanyanga, J.C., Plumb, A.A., *et al.* 2017. Diffusion-weighted imaging for evaluating inflammatory activity in Crohn's disease: comparison with histopathology, conventional MRI activity scores, and faecal calprotectin. *Abdom Radiol.,* 42:115–123.

Ream, J.M., Dillman, J.R., Adler, J., *et al*. 2013. MRI diffusion-weighted imaging (DWI) in pediatric small bowel Crohn disease: correlation with MRI findings of active bowel wall inflammation. *Pediatr Radiol., 43*(9):1077-85.

Rimola J, Alvarez-Cofino A, Perez-Jeldres T*, et al*. 2017. Comparison of three magnetic resonance enterography indices for grading activity in Crohn's disease. *J Gastroenterol.,* 52: 585–593.

Rimola J, Ord´as I, Rodriguez S et al. 2011. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. *Inflammatory Bowel Diseases.,* 17 (8): 1759–1768.

Sanka, S., Gomez, A., Set, P., *et al*. 2012. Use of small bowel MRI enteroclysis in the management of paediatric IBD. *J Crohns Colitis.,* 6:550–556.

Seo, N., Park, S.H., Kim, K.J., et al. 2016. MR enterography for the evaluation of small-bowel inflammation in crohn disease by using diffusion-weighted imaging without intravenous contrast material: a prospective noninferiority study. *Radiology.,* 278(3):762-72.

Shenoy-Bhangle, A.S., Nimkin, K., Aranson, T., Gee, M.S. 2016. Value of diffusion-weighted imaging when added to MRE evaluation of Crohn disease in children. *Pediatr Radiol.,* 46: 34–42.

Sohn, B., Kim, M.J., Koh, H., Han, K.H., Lee, M.J. 2014. Intestinal lesions in pediatric Crohn disease: comparative detectability among pulse sequences at MR enterography. *Pediatr Radiol.,* 44: 821–30.

Stojanov D, Aracki-Trenkic A, Benedeto-Stojanov D. 2016. Gadolinium deposition within the dentate nucleus and globus pallidus after repeated administrations of gadolinium-based contrast agents-current status. *Neuroradiology.,* 58(5):433-41.

Tielbeek JA, Makanyanga JC, Bipat S, et al. 2013. Grading Crohn disease activity with MRI: interobserver variability of MRI features, MRI scoring of severity, and correlation with Crohn disease endoscopic index of severity. *AJR Am J Roentgenol.,* 201: 1220–1228.

Van Assche G, Herrmann K A, Louis E *et al.* 2013. Effects of infliximab therapy on transmural lesions as assessed by magnetic resonance enteroclysis in patients with ileal Crohn'sdisease. *Journal of Crohn's and Colitis.,* 7 (12): 950–957.

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