Original Research Paper

Volume - 12 | Issue - 07 | July - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Physiology

MISMATCH NEGATIVITY IN CHILDREN DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

Dr. Rohit Saroha*	Senior Resident, Department of Physiology, Lady Hardinge Medical College University of Delhi New Delhi- India 110001. *Corresponding Author
Dr. Rajiv Bandhu	Director Professor, Department of Physiology, Lady Hardinge Medical College University of Delhi New Delhi- India 110001.
Dr. Madhulika Monga	Professor, Department of Physiology, Lady Hardinge Medical College University of Delhi New Delhi- India 110001.
Dr. Dinesh Kataria	Director Professor, Department of Physiology, Lady Hardinge Medical College University of Delhi New Delhi- India 110001.
Dr. Sunita Mondal	Director Professor, Department of Physiology, Lady Hardinge Medical College University of Delhi New Delhi- India 110001.

ABSTRACT **Objective:** Mismatch Negativity (MMN) wave of Event related brain potentials (ERPs) is a non-invasive technique to study neural activity associated with sensory and cognitive information processing. MMN is associated with pre-attentive cognitive operations. The aims of the present study were to investigate amplitude and latency of MMN wave in children with attention deficit hyperactivity disorder (ADHD) and to determine the cognitive deficits as measured by the MMN in children with ADHD. **Methodology:** This study included 28 children in the age group of 6 to 12 years. 18 children with ADHD were compared with 10 healthy age matched siblings. MMN Latency and amplitude were measured in both the groups and comparison was done. **Results:** In ADHD cases value of MMN Latency is significantly delayed at Fz, Cz , C3 and C4 as compared to the control group (Fz: 231.8 ± 12.69 vs 196.6 ± 11.53ms ,p=0.0001; Cz: 224.1 ± 11.91 vs 199.7 ±17.67 ms , p=0.0002; and C3: 226.1 ± 12.07 vs 195.2 ± 8.12 ms,p=0.0001 & C4: 226.6 ± 11.01vs 198.1 ± 6.98, p=0.0001). Moreover, In ADHD cases value of MMN amplitude is significantly reduced at Fz, Cz , C3 and C4 as compared to the control group (Fz: 3.1 ± 1.79 vs 5.1 ±1.29 µV, p=0.0059; Cz: 2.5 ± 1.47 vs 5.0 ± 2.00 µV , p=0.0008, C3: 2.1 ± 1.42 vs 5.1 ±1.37 µV, p=0.0001, and C4: 2.3 ± 1.46 vs 4.7 ± 1.89 µV, p=0.0013). **Conclusion:** It shows that in ADHD, the neurophysiologic deficits particularly in the pre attention processes in ADHD are substantial and objectively identifiable by the MMN.

KEYWORDS : ADHD, MMN , ERP

INTRODUCTION:

ADHD: According to the fifth edition of the American Psychiatric Association's (APA) DSM (DSM-V), ADHD is a behavioral and neuro-cognitive condition characterized by developmentally inappropriate and impairing levels of gross motor over activity, inattention, and impulsivity [1]. ADHD is one of the most common childhood behavioral disorders diagnosed in outpatient settings with estimated worldwide prevalence of 5.29 percent[1]. There is a high prevalence of ADHD among primary school children in India ranging from 7.2% to 11.32 % [2,3].

Children and adolescents with ADHD are either unable to maintain attention to complete a task because they lack attention control or are overly immersed in one task when they need to shift attention to another task . A meta-analysis of 6 studies suggested that ADHD children demonstrated abnormalities in MMN as shown by reduced MMN amplitude compared to healthy controls [4]. MMN is generated in the absence of behavioral responses as well as motivation and is therefore considered as indicative of pre-attentive central processing of auditory change detection. With the advantage of being independent of overt behavioral requirement, MMN has been conceptualized as an optimal electrophysiological signal to elucidate the integrity of auditory information processing with regard to the attention deficit symptoms of ADHD [5].

Small changes in the acoustic environment engage an automatic auditory-change detection mechanism reflected in the MMN. The presentation of an oddball or deviant event, embedded in a stream of repeated or familiar events, the standards, results in an evoked response that can be recorded non-invasively with electro-encephalography (EEG) and magneto-encephalography (MEG). The MMN is the negative component of the waveform obtained by subtracting the event-related response to the standard event from the response to the deviant event. The MMN is elicited by sudden changes in stimulation, peaks at about 100–250 ms from change onset and exhibits the strongest intensity in temporal and frontal areas of topographic scalp maps [6]. Given its automatic nature, the MMN might be associated with pre-attentive cognitive operations in audition and, for this reason, it has been suggested that it reflects 'primitive intelligence' in the auditory cortex [7]. MMN can be elicited even in the absence of the participant's attention, making it useful in the objective assessment of discrimination acuity of central auditory processing abilities in very young children, infants or impaired participants [8].

In the ADHD, MMN amplitudes were found to be attenuated at the central electrode and MMN latencies prolonged at the parietal electrode (Pz) relative to those in the control group. Furthermore, MMN amplitudes at Pz were negatively correlated with ADHD full-scale and hyperactivity-impulsivity and inattention subscale scores, and MMN latency at Pz was positively correlated with ADHD hyperactivity-impulsivity subscale scores. MMN reflects the severity of ADHD symptoms in children and adolescents and ADHD children show smaller P300 amplitudes and smaller MMN to auditory deviant stimuli, irrespective of relevance[5].

In a study done by Kemnner C et al[9], ADHD children showed smaller P300 amplitudes and (marginally) smaller MMN to auditory deviant stimuli, irrespective of task relevance. Rothenberger et al , showed that ADHD groups had lower MMN amplitudes compared to controls, but only the group with ADHD + Conduct Disorder (CD) suffered from a significant deficiency in automatic auditory information processing[10].

However, the review of the literature shows that very limited studies are available in which the MMN has been used to study neurophysiological changes in children with ADHD especially in the Indian context. So, the present study was planned to study the cognitive deficits as measured by the MMN component of ERPs in children with ADHD.

MATERIAL AND METHODS:

A permission from the institutional ethics committee was obtained regarding the scientific validity, research plan and ethical issues before beginning the study which was conducted between November 2016 to January 2021. A total of 37 children were recruited for the study in which there were 20 cases and 17 controls. Out of the total 37 children, 9 subjects (2 tests and 7 controls) whose MMN and P300 components

were difficult to analyze due to excessive movements were excluded from the study.

Following inclusion and exclusion criteria were applied: All newly diagnosed patients attending Psychiatry OPD fulfilling the inclusion criteria of either gender in the age range of 6 to 12 years for the study were included subject to written informed consent from the parents as approved by the institutional ethics committee. The diagnosis of ADHD was based on the DSM-V criteria. Control children were the apparently healthy siblings of the ADHD children in the age group of 6 to 12 years .For exclusion from the study , the patients with hepatic, renal, cardiovascular diseases, diabetes mellitus, cancer and systemic inflammatory disorders were excluded from the study. Similarly, the patients with Tourette's syndrome, seizure disorders, learning disabilities, autism, mental retardation, and other psychotic disorders were also excluded. Any patient having received any medication for at least two months prior to the initiation of the study and presence of any significant visual or hearing impairment were not included.

ADHD Rating Scales

Connors' parent rating scale[11]:- The short version of Connors' rating scale was used as it is the most useful diagnostic tool for ADHD because of its brevity and high accuracy. This scale has ten questions regarding the child's behavior in the last one month with four possible answers: Not at all (0), Just a little (1), Pretty much (2) and Very much (3). The questions were read one by one to the parents, and the responses were marked on the rating scale accordingly. Connors' abbreviated parent rating scale has a maximum score of 30. A score of more than 15 is suggestive of ADHD. Reduction in the score after treatment signifies clinical improvement.

Vanderbilt ADHD Parent rating scale[12]:-

The Vanderbilt ADHD Parent rating scale is based on DSM-V criteria. The scale has two components: symptom assessment and impairment in performance. On this scale the symptom assessment screens for symptoms that meet criteria for both inattentive (items 1–9) and hyperactive ADHD (items 10–18). To meet DSM-V criteria for the diagnosis, one must have at least six positive responses to either the inattentive or hyperactive symptoms or both. A positive response is marked as a 2 or 3 (often, very often). There is a place to record the number of positives in each sub-segment, and a place for the total score for the first 18 symptoms. The scale also has symptom screens for three other co-morbidities oppositional-defiant, conduct, and anxiety/ depression. To meet criteria for ADHD, there must be at least one item of the Performance set in which the child scores a 4 or 5; i.e., there must be an impairment, and not just symptoms to meet the diagnostic criteria. The scale has a place to record the number of positives (4s, 5s) and an Average Performance Score is calculated by adding the number of positives and dividing it by the number of Performance criteria answered.

MMN[13]:

Common procedure in MMN studies involves presentation of a series of identical stimuli with occasional mismatching stimuli. The mismatching stimuli can differ on any discriminable auditory dimension such as pitch, duration, intensity, or location. Hence, one of the stimuli ("standard") occurs frequently (e.g., p = .80), and the other ("deviant") occurs infrequently (p = .20). The two stimuli are usually presented at relatively short interstimulus intervals (ISI), such as 500 ms to 1 s. MMN is typically seen as a fronto-central negativity of approximately 0.5–5 (mV) in amplitude, occurring in the latency range of 100–250 ms. It exhibits a phase reversal (i.e., positive polarity) over mastoid and other lateral posterior sites over the same latency range when a nose reference is used. As the magnitude of the difference increases between the standard and deviant stimuli, the peak latency of MMN becomes progressively shorter and its peak amplitude larger. In our laboratory , the recordings were done as per guidelines issued by Duncan et al [12]. Electrophysiological study for assessment of MMN was done with SCHWARZER TOPAS EMG neurophysiologic measuring system: A 4 channel EMG/ NCV/EP system. MMN components were elicited using an auditory oddball task using 80-dB intensity sounds through headphones while subjects read books or watched any animation and asked not to pay attention to the auditory stimuli. EEG readings were recorded at the Fz, Cz, C3, and C4 positions on the scalp using disk electrodes. All electrodes were re-referenced offline to the average of two mastoid electrodes. Electrode impedance was set to less than 5 kohm. MMN was analyzed between the 50 ms prestimulus and the 360 ms post-stimulus. Artifact-free responses to stimuli were summated and averaged for EEG amplitude data. A digital 0.5- to 70-Hz band pass filter was applied to all data prior to analysis. The duration of each auditory oddball task was 250 s, and rare and frequent stimuli were presented 50 and 450 times, respectively. The MMN was identified from the difference waveform frequent minus rare as a negative wave, with a peak latency between 100 ms and 250 ms, and its latency, amplitude were recorded .

STATISTICAL ANALYSIS:

Data was coded, entered and analyzed in Graph pad prism 8.4 and SPSS version 26. The data obtained was tested for normal Gaussian distribution by using Shapiro Wilk & Kolmogrov Smirnov test and accordingly parametric and nonparametric tests were applied. For all continuous variables the data was expressed in term of mean ± S.D./S.E.M

OBSERVATIONS AND RESULTS

Both the ADHD and control group were comparable in terms of age and socioeconomic status. The mean age of ADHD group was 8.6 ± 1.81 Years and control group was 9.8 ± 1.54 years (p = 0.1083, not significant). No significant difference in the ages of children was noted in both the groups. There were 16 boys and 2 girls in ADHD group and 7 boys and 3 girls in control group. No significant difference by Chi Square test was found in group distribution (p=0.315).

The ADHD and control groups differed highly significantly in Connors test scores as shown by Mann Whitney test (ADHD group median 23.0, control group median 9.0, P value <0.0001). ADHD group showed inattentive symptoms in 14 subjects (77.8%), hyperactivity in 16 subjects (89 %), anxiety-depressive symptoms in 4 subjects (22.2%) and conduct disorder in 11 subjects (61%). Impulsive and inattentive combined symptoms were shown in 12 subjects (67%).

Table 1: Statistical analysis of the MMN latency values between ADHD group and Control group of children

S. No	Parameter	ADHD Group (Mean ± SD) N=18	Control Group (Mean ± SD) N=10	P value
1	MMN Fz latency (ms)	231.8 ± 12.69	196.6 ± 11.53	<0.0001
2.	MMN Cz latency (ms)	224.1 ± 11.91	199.7 ± 17.67	0.0002
3	MMN C3 latency (ms)	226.1 ± 12.07	195.2 ± 8.12	<0.0001
4.	MMN C4 latency (ms)	226.6 ± 11.01	198.1 ± 6.98	<0.0001

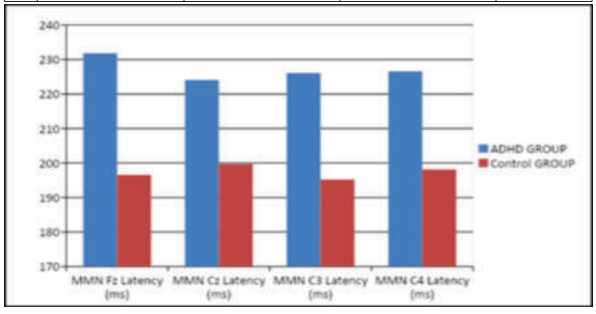

Figure 1: Bar diagram showing the MMN latency values comparison between ADHD group and Control group of children

Table 1 and Figure 1 show significant differences in the MMN Latencies recorded at Fz, Cz , C3 &, C4 among ADHD & normal controls.In ADHD cases value of MMN Latency is significantly delayed at Fz, Cz , C3andC4 as compared to the control group (Fz: 231.8 ± 12.69 vs 196.6 ± 11.53ms ,p=0.0001; Cz: 224.1 ± 11.91vs 199.7 ± 17.67ms , p=0.0002; and C3: 226.1 ± 12.07 vs 195.2 ± 8.12ms,p=0.0001 & C4: 226.6 ± 11.01vs 198.1 ± 6.98, p=0.0001)

Table 2: Statistical Analysis Of The MMN Amplitude Values Between ADHD Group And Control Group Of Children

S. No	Parameter	ADHD Group (Mean ± SD) N=18	Control Group (Mean ± SD) N=10	P value
1	MMNFz amplitude (μV)	3.17 ± 1.79	5.10 ±1.29	0.0059

2.	MMNCz amplitude (μV)	2.50 ±1.47	5.00 ± 2.00	0.0008
3	MMNC3 amplitude (μV)	2.17 ± 1.42	5.10 ± 1.37	<0.0001
4.	MMNC4 amplitude (μV)	2.39 ±1.46	4.70 ± 1.89	0.0013

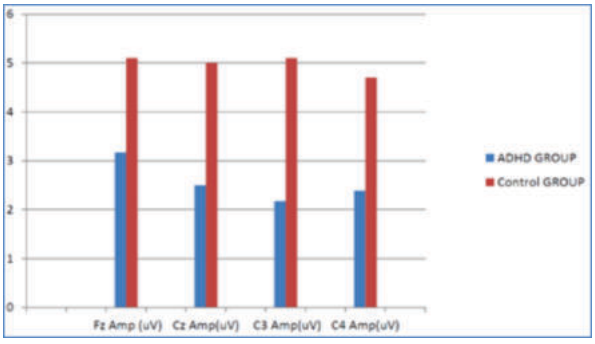

Figure 2: Bar diagram showing the MMN Amplitude values comparison between ADHD group and Control group of children

RESULTS :

Table 2 and Figure 2 show significant difference in the MMN Amplitudes recorded at Fz, Cz , C3&, C4 among ADHD & normal controls. In ADHD cases value of MMN amplitude is significantly reduced at Fz, Cz, C3andC4 as compared to the control group (Fz: 3.1 ± 1.79 vs 5.1 ±1.29 μV, p=0.0059; Cz: 2.5 ±1.47 vs 5.0 ± 2.00 μV , p=0.0008, C3: 2.1 ± 1.42 vs 5.1 ±1.37 μV, p=0.0001, and C4: 2.3 ±1.46 vs 4.7 ± 1.89 μV, p=0.0013)

DISCUSSION:

In this study the mean of MMN amplitude in the ADHD group was significantly smaller than that in the control group at Fz, Cz, C3, and C4. Also, it was found that the mean latency in ADHD group was significantly longer than that in the control children group at Fz , Cz , C3 and C4. In a similar study waveform abnormalities in the latency range of control MMN suggested either a decrease in MMN amplitude or an increase in MMN latency in hyperactive subjectswith a trend toward normalization by methylphenidate, suggestive of information-processing abnormalities among hyperactive children that may be sensitive to methylphenidate therapy[14]. In another study ADHD children showed smaller P3 amplitudes and (marginally) smaller MMN to auditory deviant stimuli, irrespective of task relevance [9].

KiepelaainenR[15] studied MMN in easily distractible (n = 20) and in non-distractible (n = 20) healthy 9-year-old children. Two MMN phases were revealed in both groups: an earlier MMN peak at approximately 220 ms and a later negative slope approximately 300-500 ms after stimulus presentation. Their results suggested a strong frontal lobe contribution in the generation of the later MMN phase, and this response was significantly reduced in amplitude in the distractible children. This suggested that distractible children may have deficits in the frontally mediated aspects of auditory sensory memory[15]. As the MMN indexes different types of central auditory abnormalities in different neuropsychiatric, neurological, and neurodevelopmental disorders, the diminished amplitude/prolonged peak latency observed in patients usually indexes decreased auditory discrimination. Furthermore, MMN deficit may also index cognitive and functional decline or deficits shared by different disorders irrespective of their specific aetiology and symptomatology[16].

In a study by Lee et al [17], they assessed the associations between the MMN amplitude and latency with ADHD symptom severity in medication-naïve children and adolescents. Their results showed that the more severe the ADHD symptoms, the lower the amplitude and the longer the latency of the MMN wave. Moreover, the MMN amplitude difference according to the severity of ADHD symptoms between the ADHD group and the subclinical ADHD group was significant at FCz, and the MMN latency difference was significant at Fz and FCz. The K-ARS-IV, K-ARS-In, and K-ARS-H scores in the ADHD group were also significantly and strongly negatively correlated with MMN amplitude at Cz and CPz[17]. Yamamuro k et al [5] measured the amplitude and latency of MMN in ERPs and assessed correlations with the clinical severity of ADHD, as measured by the ADHD Rating Scale IV - Japanese version. Participants were 51 treatment-naïve children and adolescents with ADHD (mean age 10.42±3.35 years) and 15 normally developing age- and sex-matched children (mean age 11.8±3.36 years). In the ADHD group, MMN amplitudes were attenuated at the central electrode and MMN latencies prolonged at the parietal electrode (Pz) relative to those in the control group. Furthermore, MMN amplitudes at Pz were negatively correlated with ADHD full-scale and hyperactivity-impulsivity and inattention subscale scores, and MMN latency at Pz was positively correlated with ADHD hyperactivity-impulsivity subscale scores. This suggests that MMN reflects the severity of ADHD symptoms in children and adolescents, and provides support for the use of ERPs in evaluating ADHD symptoms in patients [5].

Zhang et al, investigated the preattentive change detection in preschool children with ADHD, wherein they compared the MMN and P3a of ERP between preschool ADHD and normal children using three-stimulus oddball paradigm. Analyzing MMN and P3a components, they found that MMN elicited by deviants and P3a elicited by novelty were significantly reduced in patients than in controls. In addition, the P3a amplitude was positive correlated to IQ and negatively correlated to hyperactivity, antagonistic defiance and conduct problems in Swanson, Nolan, and Pelham IV Rating Scale, parent version [18]. Therefore the findings in our study on MMN in children diagnosed with ADHD corroborate with the various recent and earlier national and international publications wherein the deficit in preattention processes in ADHD children is observed as shown by the delayed latencies as well as reduced amplitude of MMN waves in all the electrodes.

REFERENCES:

1. Epstein JN, Loren RE. Changes in the Definition of ADHD in DSM-5: Subtle but Important. Neuropsychiatry (London). 2013 Oct 1;3(5):455-458. doi: 10.2217/npy.13.59. PMID: 24644516; PMCID: PMC3955126
2. Juneja M, Sairam S, Jain R, Attention deficit hyperactivity disorder in adolescent school children, Indian Pediatr. 2014 Feb; 51(2):151-2.
3. Venkata JA, Panicker AS. Prevalence of Attention Deficit Hyperactivity Disorder in primary school children. Indian J Psychiatry. 2013 Oct;55(4):338-42. doi: 10.4103/0019-5545.120544. PMID: 24459303; PMCID: PMC3890923.
4. Cheng CH, Chan PS, Hsieh YW, Chen KF. A meta-analysis of mismatch negativity in children with attention deficit-hyperactivity disorders. NeurosciLett. 2016 Jan 26;612:132-137. doi: 10.1016/j.neulet.2015.11.033. Epub2015 Nov 25. PMID: 26628248.
5. Yamamuro K, Ota T, Iida J, Nakanishi Y, Kishimoto N, Kishimoto T. Associations between the mismatch-negativity component and symptom severity in children and adolescents with attention deficit/hyperactivity disorder. Neuropsychiatr Dis Treat. 2016 Dec 12;12:3183-3190. doi: 10.2147/NDT.S120540. PMID: 28003754; PMCID: PMC5161404.
6. Sams M, Paavilainen P, Alho K, Näätänen R. Auditory frequency discrimination and event-related potentials. Electroencephalography and Clinical Neurophysiology/ Evoked Potentials Section. 1985 Nov 1;62(6):437-48.
7. Näätänen R, Tervaniemi M, Sussman E, Paavilainen P, Winkler I. 'Primitive intelligence'in the auditory cortex. Trends in neurosciences. 2001 May 1;24(5):283-8.
8. Puente A, Ysunza A, Pamplona M, Silva-Rojas A, Lara C. Short latency and long latency auditory evoked responses in children with attention deficit disorder. Int J PediatrOtorhinolaryngol 2002;62:45–51.
9. KemnerC ,Verbaten MN , Koelega HS et al . Event related brain potentials in children with ADHD : effects of stimulus deviancy and task relevance in the visual and auditory modality. Bill psychiatry 1996; 40(6) ; 522 – 534
10. Rothenberger A, Banaschewski T, Heinrich H, Moll GH, Schmidt MH, Klooster B. Co-morbidity in ADHD-children: effects of coexisting conduct disorder or tic disorder on event-related brain potentials in an auditory selective-attention task, Eur. Arch. Psychiatry Clin. Neurosci. 2000; 250:101–110.
11. ConnersCK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol. 1998 Aug;26(4):257-68. doi: 10.1023/a:1022602400621. PMID: 9700518.
12. Mark L. Wolraich, MD, Warren Lambert, PhD, Melissa A. Doffing, MA, Leonard Bickman, PhD, Tonya Simmons, BS, Kim Worley, MD, Psychometric Properties of the Vanderbilt ADHD Diagnostic Parent Rating Scale in a Referred Population, Journal of Pediatric Psychology, Volume 28, Issue 8, December 2003, Pages 559–568, https://doi.org/10.1093/jpepsy/jsg046
13. Duncan CC, Barry RJ, Connolly JF, Fischer C, Michie PT, Näätänen R, Polich J, Reinvang I, VanPetten C. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clinical Neurophysiology. 2009 Nov 1;120(11):1883-908.
14. WinsbergBG ,Javitt DG, SilipoGS , Doneshka P . Mismatch negativity in hyperactive children; effects of methyl phenidate dose. Psychopharma.Col Bull 1993; 29
15. KiepelaainenR ,Partanen j , Karhu J. Reduced mismatch negativity suggests deficits in pre attentive auditory processing in distractible children . Neuroreport 1999; 10(16)
16. Näätänen R, Kujala T, Escera C, Baldeweg T, Kreegipuu K, Carlson S, Ponton C. The mismatch negativity (MMN)–a unique window to disturbed central auditory processing in ageing and different clinical conditions. Clinical Neurophysiology. 2012 Mar 1;123(3):424-58.
17. Lee YJ, Jeong MY, Kim JH, Kim JS. Associations between the Mismatch-negativity Potential and Symptom Severity in Medication-naïve Children and Adolescents with Symptoms of Attention Deficit/hyperactivity Disorder. ClinPsychopharmacolNeurosci. 2020 May 31;18(2):249-260. doi: 10.9758/cpn.2020.18.2.249. PMID: 32329306; PMCID: PMC7242107.
18. Zhang, Jinsonga; Qiu, Meihuia; Pan, Jingxuea; Zhao, Lunb The preattentive change detection in preschool children with attention deficit hyperactivity disorder: a mismatch negativity study.,NeuroReport: July 10, 2020 - Volume 31 - Issue 10 - p 776-779doi: 10.1097/WNR.0000000000001472