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Association of attention deficit disorder with bedside anti-saccades in survivors of childhood leukemia

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Abstract

Impaired attention is well recognized in childhood cancer survivors. We prospectively evaluated 162 long-term survivors of childhood acute lymphoblastic leukemia to study an association between presence of neurologic soft signs as measured by Zurich Neuromotor Scale, bedside evaluation of antisaccades, and attention deficit disorder. Attention deficit disorder was recognized in 10.5% of the study cohort. We did not find an association of attention deficit with presence of any soft sign. However, there was an association between presence of abnormal anti-saccades and attention deficit ($p=0.04$). These results will require further validation and if confirmed may introduce a quick bedside method of assessing impaired attention in cancer survivors.

Keywords

Attention deficit disorder; childhood; acute lymphoblastic leukemia; anti-saccades; soft signs

Introduction

Approximately 10% of USA adolescents have attention deficit hyperactivity disorder (ADHD),¹ often accompanied by abnormalities in fine motor function (soft signs) and pro and anti-saccade eye movements.^{2,3} Initiation of reflex target seeking visual saccade involves the anterior cingulate, thalamus, anterior insula, and dorsolateral prefrontal cortices, while inhibition of this reflex target seeking eye movement and production of voluntary contraversive eye movement (anti-saccades) involves parietal and medial temporal structures.⁴ Traditional assessment of anti-saccades require sophisticated equipment to

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Authorship Contribution: Dr. Khan conceived and wrote the protocol and manuscript. Drs. Hudson helped in developing the protocol. Dr. Ness managed and cleaned the data. Drs. Zhu and Srivastava are the statisticians, and all authors helped in reviewing data and editing of the manuscript.

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record inhibition of reflexive eye movement and production of an opposite mirror movement, which is not incorporated into routine clinical practice.

Many childhood acute lymphoblastic leukemia (ALL) survivors have impaired attention and motor movement and we have previously reported presence of ADHD in this population.^{5,6} In this study of ALL survivors, we explored associations of ADHD with neurologic soft signs and bedside anti-saccade testing. To our knowledge, anti-saccade eye movements have never before been evaluated with a bed side technique.

Methods

This institutionally review board approved protocol involved a cross-sectional study of childhood ALL survivors who were English speaking, at least five years from cancer diagnosis, and at least one year off cancer therapy. Informed consent was obtained from survivors or parents. Methodological details have been previously published.⁶ In brief, a trained investigator administered a structured questionnaire to all participants. This questionnaire included 18 symptoms of attention deficit and hyperactivity disorder consistent with Vanderbilt Parent Rating Scale.⁷ This was followed by a face to face evaluation by the study neurologist where each participant was evaluated with standardized examination. Neurologic soft signs were tested as defined by Zurich neuromotor scale,⁸ with the addition of two procedures discussed below. Karnofsky performance scale was assigned to each participant. Modified Mini Mental Status questionnaire was used to assess cognitive ability.⁹ This is scored 0–100 with lower numbers suggesting cognitive impairment.

Anti-saccades were tested with the survivor seated comfortably facing the examiner at arm's length with eyes at the same level. The participant was asked to fixate on the examiner's eyes while the examiner's arms were extended with hands at half distance between the survivor and examiner. The examiner then randomly snapped fingers on either hand for a total of 10 stimuli and the participant was required to quickly look to the opposite hand with each stimulus. Participant returned the gaze to the examiner's eyes on a verbal "back" command. The next stimulus was given soon after return of the participant's gaze to fixation. Rapidity of the response and initial eye movement were noted. Any eye movement ipsilateral to the stimulus was considered an error. Instruction and demonstration by examiner followed by trial anti-saccades to make sure the participant understood instructions preceded the test. The participant's response of normal latency and no error was scored as (0), delayed initiation of anti-saccade without an error (1), 2–4 (occasional) errors as 2, and 5 (frequent errors) as 3.

Sequential hand movements were evaluated with the participant seated comfortably with hands resting over thighs. The examiner demonstrated and then asked the participant to perform 10 sets of sequentially tapping their thighs with palm, edge and fist position of the hand on either side. Movements were not timed and were scored as normal (0), mildly/perceptibly irregular (1), grossly/markedly irregular (2), or inability to perform (3).

ADHD was established using a study questionnaire based on DSM-IV criteria. Association of ADHD with neuromotor soft signs, sequential hand movements, and anti-saccades was

evaluated with logistic regression. For statistical analyses anti-saccades were categorized as normal (0) versus abnormal (1–3).

Results

There were 90 male and 72 female participants. Median age at study enrollment was 15.7 years (range 6.9–29.0) and median time from completion of ALL therapy was 7.4 years (1.9–20.3). History of leukemia relapse was present in 5%, CNS leukemia at diagnosis in 24%, all received triple intrathecal chemotherapy (hydrocortisone, cytarabine and methotrexate), and 14% were treated with craniospinal radiation. Seventeen (10.5%) of 162 participants were diagnosed with ADHD: 8.7% had inattentive; 0.6% hyperactive; and 1.2% combined types. A vast majority (97%) scored 80 out of 100 on modified mini mental status questionnaire suggesting good cognitive function. Only one participant scored 90 on Karnofsky performance scale. No one had visual or hearing deficits. Only presence of abnormal antisaccades was associated with ADHD ($p=0.04$; Table 1), with the association primarily in those with purely inattentive type ($p=0.0004$).

Discussion

This study suggests utility of the bed-side anti-saccade testing technique. Abnormal anti-saccades were strongly associated with the inattentive type of ADHD, the most common type identified in ALL survivors. Impairment of attention and processing time in childhood ALL survivors is not uncommon.⁵ Bedside testing of anti-saccades takes less than two minutes and if confirmed in further studies this technique may be useful to screen cancer survivors in clinic for pervasive attention deficits.

There are many inherent weaknesses in our study. This study did not have a control group and formal neuropsychological testing was not obtained. However, DSM-IV criteria were applied to standard ADHD questionnaire asked by the examiner. Lack of formal neuropsychological assessment makes controlling for additional cognitive deficits not possible. However, a vast majority of participants scored very high on mini mental status examination questionnaire.

Bed side technique for assessing anti-saccades will need validation against either laboratory based analysis, or against formal neuropsychological assessment and functional neuroimaging. We are currently studying bedside anti-saccade assessment in different tumor populations with formal neuropsychological testing, control group, and advanced neuroimaging. Further studies will also define clinically relevant degrees of abnormality on anti-saccades as some children with abnormal antisaccades in our cohort did not fulfill ADHD diagnostic criteria. If confirmed, this technique may be studied and applied to non-cancer populations as well.

Contrary to non-cancer children with ADHD,² we did not find an association between ADHD and neurological soft signs. This discrepancy is likely because the stimulus for ADHD in our cohort was cancer treatment rather than an underlying neurodevelopmental condition present from birth.

In conclusion, abnormal bedside testing of anti-saccades may indicate presence of impaired attention in survivors of childhood ALL and needs further validation. If confirmed it may become a quick screening tool for ADHD in cancer survivors.

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Ethical approval: This study was approved by the Institutional Review Board of St. Jude Children's Research Hospital before patient enrollment began. All participants provided informed written consent.

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Frequency of abnormal soft signs and anti-saccades and univariate logistic regression analysis (present versus absent) of their association with attention deficit hyperactivity disorder in survivors of childhood acute lymphoblastic leukemia (n=162)

Table 1

Abnormal neurologic signs	ADHD present	ADHD absent	Odds Ratio	95% Confidence Interval	P-value
Hand pronation/supination	5.9%	10.5%	0.53	0.07 – 4.31	0.56
Finger tapping	5.9%	3.5%	1.73	0.19 – 15.7	0.63
Repetitive hand motion	11.8%	5.6%	2.25	0.44 – 11.58	0.33
Foot tapping	5.9%	9.8%	0.58	0.07 – 4.68	0.61
Static balance	5.9%	12.6%	0.43	0.05 – 3.47	0.43
Tongue movement	11.8%	4.2%	3.05	0.56 – 16.45	0.2
Sequential hand	47.1%	37.2%	1.5	0.54 – 4.13	0.43
Anti-saccades	37.5%	15.8%	3.2	1.05 – 9.75	0.04

Abbreviations: ADHD = Attention deficit and hyperactivity disorder