MEDICAL HYPOTHESIS

Disconnections in Infantile-Onset Saccade Initiation Delay: A Hypothesis

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ABSTRACT: Infantile-onset saccade initiation delay (ISID), commonly known as congenital ocular motor apraxia, is characterized by difficulty in triggering horizontal volitional saccades. It typically presents with head thrusts in infancy and is often associated with developmental delay. Patients with ISID are reported to have abnormalities in various brain regions including the corpus callosum, brainstem, and cerebellum. We propose that ISID is caused by the disruption or disconnection of axons linking analogous brain regions involved in processing saccades across the two sides of the brain or bilateral damage to these regions.

RÉSUMÉ: Hypothèse concernant les déconnexions dans le délai dans le déclenchement des saccades dans la petite enfance. Le délai dans le déclenchement des saccades qui commence dans l'enfance (DDSE), connu sous le nom d'apraxie oculomotrice congénitale, est caractérisé par une difficulté à déclencher des saccades volontaires horizontales. On l'observe de façon typique lors de mouvements brusques de la tête chez les nourrissons et il est souvent associé à un retard de développement. Des anomalies dans différentes régions du cerveau ont été rapportées chez les patients qui présentent un DDSE, dont le corps calleux, le tronc cérébral et le cervelet. Nous émettons l'hypothèse que le DDSE est dû à une perturbation ou à une déconnexion des axones qui relient des régions analogues du cerveau qui sont impliquées dans le traitement des saccades entre les deux hémisphères ou à un dommage bilatéral dans ces régions.

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Infantile-onset saccade initiation delay (ISID), commonly known as congenital ocular motor apraxia, is characterized by difficulty in triggering horizontal saccades on command in either direction while maintaining the ability to generate horizontal smooth ocular pursuit and vertical eye movements.[1,2] Eye movement recordings in ISID may show hypometric saccades in addition to the increase in horizontal saccadic latency.[3] Saccadic velocity is typically normal.[4,5] To overcome the difficulty in initiating saccades, infants use head thrusts or eye blinks to rapidly change the direction of gaze.[6] Reflexive saccades, including the fast phases of the optokinetic response and vestibulo-ocular reflex, may be impaired.[3,4,7] Hence, the appropriateness of the term 'ocular motor apraxia' has been questioned,[1,7,8] because by definition, apraxia consists of impaired volitional movements in response to commands in the presence of intact reflexive movements.[8] The term "intermittent saccade failure" has been suggested as a better description of this clinical finding.[1] We suggest that the term 'congenital' is inappropriate since the diagnosis of ISID is not made at or soon after birth but when head thrusts appear at four to six months of age or later. We suggest using the term 'infantile-onset' instead, because the condition manifests itself during infancy and the diagnosis is usually made during infancy or later. We propose that delay rather than failure of saccade initiation better describes the disorder.

Infantile-onset saccade initiation delay is a clinical finding in several disorders and is often associated with developmental delay.[2,6,9,10] The etiology of ISID is unknown. Neuroradiological findings in ISID are diverse. The most common is cerebellar hypoplasia, especially of the inferior vermis.[2,3,6,7,10] Other reported abnormalities include agenesis or hypoplasia of the corpus callosum,[1,3,9,11] and tumors or cysts in the posterior fossa.[3,10,12] Neuroimaging studies may also be normal.[6] Bilateral frontal and parietal lobes lesions cause 'acquired ocular motor apraxia',[12] which will be referred to in this article as acquired SID. The main focus of this paper is on ISID.

Hypothesis

We propose that the fundamental problem in ISID is a developmental disruption or disconnection of axons linking analogous brain regions involved in processing saccades across the two sides of the brain or bilateral damage to these regions. Acquired bilateral damage to saccadic motor regions may also explain the acquired forms of SID. In order to initiate saccades, we suggest that saccadic signals in one brain region need to be

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synchronized with appropriate saccadic signals in the contralateral region such that excitatory signals will lead to activation of the agonist muscles, while inhibitory signals will lead to relaxation of the antagonist muscles, thus facilitating the initiation of saccades in the desired direction. The axons connecting these saccadic ocular motor regions must be important in coordinating this task. Bilateral activation of the frontal eye fields (FEFs) and cerebellum seen on fMRI during saccades,[13,14] is consistent with our proposal. The increased activity on fMRI results from an increase in blood flow to activated brain regions due to their increased metabolic demands. Either excitatory or inhibitory neuronal activity can lead to the increased signal seen on fMRI.[15] If there is a conflict in the signals reaching the agonist and antagonist extraocular muscles, then SID occurs with increased saccadic latency. When saccadic latency is significantly prolonged, head thrusts or blinks are used as strategies to help initiate saccades. We propose that the presence of intermittent saccades (as opposed to the total absence of saccades) in some ISID patients,[1] suggests that on some occasions the saccadic latency is not so severely prolonged as to require blinks or head thrusts to speed up saccadic initiation.

We discuss our hypothesis further in relation to commonly described MRI abnormalities in patients with ISID and suggest future directions for research based on testable hypotheses.

The corpus callosum

Complete or partial agenesis of the corpus callosum has been reported in children with ISID.[1,9,11] In 1979, Orrison proposed that defective interhemispheric transfer of visual information may be important in the pathogenesis of ISID.[11] We suggest that defective transfer of ocular motor signals between the FEFs and between the parietal eye fields (PEFs), both important structures for the generation of saccades, is the underlying problem in ISID in these patients. Using the double step saccade task, the interhemispheric transfer of updated spatial information following saccades across the visual hemifields was reported to be temporarily impaired in split-brain monkeys.[16] This was manifested by saccadic inaccuracies and increased saccadic latencies.[16] Updating activity in the PEFs is also modified in the split-brain monkey because across-hemifield signals are reduced in magnitude and delayed in onset compared to within-hemifield signals, which indicates that the pathways for across-hemifield updating are less effective in the absence of the forebrain commissures.[17]

However, ISID is not commonly reported in patients with partial or complete agenesis of the corpus callosum.[9,18] Since as many as 47% of cases of ISID do not have associated head thrusts,[3] and since some patients with agenesis of the corpus callosum can be missed in the absence of other abnormalities,[19] we suggest that ISID may be more common in patients with partial or complete agenesis of the corpus callosum than is currently known. The initiation delay may be subtle and overlooked, especially if children use eye blinks only to initiate saccades. In addition, not all cases of partial agenesis of the corpus callosum affect axons connecting the FEFs and PEFs. Fibers connecting the FEFs and PEFs mainly, though not exclusively, cross at the body of the corpus callosum and splenium respectively.[20] We suggest that disruption of these fibers results in ISID. It appears likely that for ISID to occur, interhemispheric disconnection between both FEFs and PEFs are needed to produce ISID. We did not find large systematic studies with detailed eye movement examination or recordings in patients with intractable epilepsy who had corpus callosotomy. These callosotomy patients would be interesting to investigate to test our hypothesis. One study reported two corpus callosotomy patients who had eye movement recordings and were able to generate saccades.[21] However, saccadic latencies were not reported. Another study on a callosotomy patient reported longer saccadic latencies than a normal control.[22] Several factors need to be considered when investigating such patients including the extent and completeness of the callosotomy and other interhemispheric commissures, time since surgery, and the capacity to transfer ocular motor saccadic information between the two cerebral hemispheres using other cortical or subcortical connections that may otherwise be normally redundant.[23]

The frontal and parietal eye fields

The FEFs and PEFs are important for the generation of saccades.[24] Bilateral lesions of the FEFs or PEFs result in modest and temporary saccadic initiation and accuracy deficits.[24,25] The saccadic defect is profound when both FEFs and PEFs are lesioned.[25] In monkeys, bilateral lesions of the FEFs are associated with temporary but pronounced deficits in saccades aimed at peripheral targets, which appears like a neglect syndrome.[25] Cerebral hemidecortication to control severe epilepsy is associated with increased saccadic latencies in both horizontal directions several years after the surgical procedure is performed.[26] Stimulation of one FEF is associated with excitatory activity in some cells as well as inhibitory activity in other cells in the contralateral FEF.[27] A consensus between excitatory and inhibitory cell activities in the FEFs occurs to produce the desired eye movement such that agonist extraocular muscles are activated while antagonist extraocular muscles are silenced.[27] The FEFs are activated bilaterally during saccades on fMRI.[13] Functional impairment or structural abnormalities involving both FEFs and PEFs may therefore explain the acquired and infantile-onset forms of SID respectively. In summary, several cerebral regions involved in processing saccades must be impaired before profound SID becomes clinically apparent, likely due to saccadic neural pathway redundancy. Physiologically, a direct cerebral disconnection between saccadic regions may lead to inappropriate signals to the agonist and antagonist extraocular muscles, which manifests as SID. Another mechanism may involve impaired transfer of signals through descending projections from these regions to the superior colliculi or other regions of the brainstem such as omnipause cells (Dr. David M. Waitzman, personal communication), which results in bilateral loss of cerebral modulation on saccade trigger circuitry in the brainstem.

The cerebellum

Horizontal and vertical 'ocular motor apraxia' is a feature of Joubert syndrome and related disorders (JSRD).[28,29] The cerebellar vermis is hypoplastic and the characteristic molar tooth sign on MRI is caused by thickened and elongated superior cerebellar peduncles and a deep interpeduncular fossa.[28] The absence of decussation of the superior cerebellar peduncles is reported on tractography,[29] and neuropathology.[30] There is an

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absence of crossing of commissural fibers within the vermis and other tracts in the brainstem.[29] In addition, the deep cerebellar nuclei are displaced laterally and the fastigium is shifted rostrally.[31] A midline cleft separates the cerebellar hemispheres.[29,31]

The posterior cerebellar vermis (lobules VI and VII) and the ocular motor region of the fastigial nuclei are important in processing saccades.[14] The former is absent and the latter is abnormal in JSRD. The output signals within the abnormally formed vermis and through the superior cerebellar peduncles do not cross. We suggest that this is the reason for the 'ocular motor apraxia' reported in JSRD. The gene product of one of the abnormal genes (known as AHI1) in JSRD gives rise to decussating tracts in the cerebellum and cerebral cortex and is thought to have a role in modulating axonal decussation.[32]

The role of the cerebellum in ISID has been questioned by the absence of 'ocular motor apraxia' in all patients with cerebellar hypoplasia or in patients whose cerebellum has been removed.[7] We suggest that ISID occurs only if there is disruption in the decussation of axons carrying saccade-related signals, within the vermis and its output tracts with loss of their modulating influence on saccadic regions in the brainstem. Hence, not all patients with cerebellar hypoplasia will have ISID. Removal of the whole cerebellum eliminates an important part of the saccadic network that predominantly process saccade accuracy. Surgical splitting of the vermis used to be commonly performed in patients with posterior fossa tumors. We did not find systematic studies with detailed eye movement examination or recording of saccadic latencies in patients with split vermis. One study documented saccadic overshoot dysmetria in eight patients with cerebellar tumors and vermis-splitting surgery.[33] In three patients, visually-guided saccadic latency was recorded and was found to be within the normal range. However, saccades to command were not recorded in that study. In addition, it is not possible to separate the effects of the cerebellar tumor from vermis-splitting on saccade parameters in these patients.

The superior colliculus commissure

Lesions in the superior colliculus cause increased saccadic latency and hypometria.[34] Bilateral activation of the superior colliculus on fMRI is reported in humans during saccades with contralateral dominance of activity to saccadic direction.[35] A thin intercollicular commissure in a child with ISID is reported in this issue of the journal. His findings are consistent with our disconnection hypothesis. The mechanism of SID in this case may be through the loss of reciprocal inhibition between the two superior colliculi.[36]

The fourth ventricle

Dilation of the fourth ventricle has been reported in ISID.[2] We suggest that fourth ventricular dilation is a manifestation of underlying abnormalities involving the interruption of decussating fibers carrying saccade-related signals in that region.

Normal brain MRI

In patients with ISID and 'normal' brain imaging, we propose that the underlying abnormality is beyond the resolution of the current MRI techniques. We suggest that these patients should be investigated further using MRI tractography.

ISID and vertical saccades

Reports of ISID affecting the initiation of vertical saccades only are rare but have been described.[37] In JSRD and in acquired 'ocular motor apraxia', patients typically have difficulties initiating both vertical and horizontal saccades.[12,28] One study reported vertical ISID using eye movement recording in an asymptomatic individual.[19] It remains to be seen whether subtle or subclinical vertical ISID accompanies the 'classical' horizontal ISID. Familiarity with vertical saccades developmental trajectory and their wide variability in childhood,[38] together with eye movement recordings will be needed to answer this question. Our disconnection hypothesis predicts that vertical ISID is more prevalent than previously appreciated in patients with horizontal ISID.

ISID, head thrusts and blinks

The use of head thrusts and blinks to facilitate saccades in children with ISID is well documented.[1] Head thrust is not commonly reported in adults with SID, perhaps due to its awkward social appearance. The absence of head thrusts does not rule out the presence of ISID and head thrusts are not diagnostic of ISID.[3] Head thrusts may occur in disorders that cause slow or significantly hypometric saccades.[39,40] We suggest that ISID is more common than is currently recognized because of the over reliance on the presence of head thrusts to diagnose ISID. We also propose that blinks are used to initiate saccades in these patients only when saccadic latency is significantly prolonged and that mild increase in saccadic latency from any cause may not necessarily be accompanied by blinks (or head thrusts). This hypothesis can easily be tested by careful eye movement examination to ascertain if blinks accompany every saccade in patients with various degrees of prolonged saccadic latency.

The natural history of ISID

The natural history of ISID is unknown. It is believed that it improves with age,[11] but this is not proven. The strategy for initiating saccades change from head thrusts to blinks with increasing age.[1] It is unknown whether saccadic latency decrease or even normalizes with increasing age as the saccadic circuitry matures. A longitudinal study with eye movement recordings in patients with ISID is needed to answer this question.

'Ocular motor apraxia' is a misnomer in some diseases

'Ocular motor apraxia' is a commonly reported feature in ataxia telangiectasia and has also been reported in Gaucher disease.[1] Saccade velocity is slow in these disorders due to brainstem involvement, and hence the saccadic abnormality is not a true 'apraxia' or impairment in triggering saccades, which usually causes an increase in saccade latency. The so-called 'ocular motor apraxia' in both ataxia-oculomotor apraxia types 1 and 2, is also not a true 'apraxia', because saccades are hypometric with typically normal latencies.[39,40] The normal saccadic latency means that it is not a true apraxia since saccadic initiation is normal. Our disconnection hypothesis applies only to patients with SID.

Finally, most of the reported 'acquired and congenital ocular motor apraxias' are not genuine 'apraxias', because the initiation

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of the fast phases of the vestibulo-ocular reflex or optokinetic response (i.e., reflexive saccades) is also impaired (in addition to volitional saccadic impairment) in the majority of these patients.[1,12] We suggest reserving the term 'ocular motor apraxia' (either early-onset or the acquired form) to patients with impaired volitional saccades but intact reflexive saccades.

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