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Ocular motor anatomy in a case of interrupted saccades

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Abstract

Saccades normally place the eye on target with one smooth movement. In late-onset Tay—Sachs (LOTS), intrasaccadic transient decelerations occur that may result from (1) premature omnipause neuron (OPN) re-activation due to malfunction of the latch circuit that inhibits OPNs for the duration of the saccade or (2) premature inhibitory burst neuron (IBN) activation due to fastigial nucleus (FN) dysregulation by the dorsal cerebellar vermis. Neuroanatomic analysis of a LOTS brain was performed. Purkinje cells were absent and gliosis of the granular cell layer was present in the dorsal cerebellar vermis. Deep cerebellar nuclei contained large inclusions. IBNs were present with small inclusions. The sample did not contain the complete OPN region; however, neurons in the OPN region contained massive inclusions. Pathologic findings suggest that premature OPN re-activation and/or inappropriate firing of IBNs may be responsible for interrupted saccades in LOTS. Cerebellar clinical dysfunction, lack of saccadic slowing, and significant loss of cerebellar cells suggest that the second cause is more likely.

Keywords

fastigial nucleus; omnipause neurons; burst neurons; latch circuit; brainstem

Introduction

Late-onset Tay—Sachs (LOTS) is a predominantly cerebellar, autosomal recessive disorder of sphingolipid metabolism with intracerebral GM2 ganglioside accumulation (inclusions) caused by deficiency of the enzyme hexosaminidase A. Saccades in LOTS are interrupted by transient decelerations, during which velocity abruptly declines but generally remains greater than 50°/s (Rucker et al., 2004). Normal initial velocity suggests integrity of excitatory burst neurons (EBNs) and motoneurons. Interrupted saccades may be due to (1) premature omnipause neuron (OPN) re-activation due to malfunction of the latch circuit that inhibits OPNs for the saccade duration or (2) premature inhibitory burst neuron (IBN) activation due to fastigial nucleus (FN) dysregulation by the dorsal cerebellar vermis.

Methods

Three brainstem and cerebellar tissue blocks in 20% formalin from a patient with LOTS were obtained from the Brain and Tissue Bank for Developmental Disorders (Baltimore, MD) under contracts NO1-HD-3368 and NO1-HD-4-3383. Axial brainstem and parasagittal cerebellar sections were stained with Nissl for highlighting neuronal cytoarchitecture and glia, Luxol Fast Blue (LFB) for cell bodies and fibres, and Holzer for glial fibres and detection of gliosis. Brainstem sections were processed for immunocytochemical detection of parvalbumin (PAV), glycine transporter, and synaptophysin.

Results

There was nearly complete loss of Purkinje cells and severe atrophy of the granular cell layer throughout lobules I–IX, including the dorsal cerebellar vermis (Fig. 1A). Diffuse gliosis was seen in white matter underlying the Purkinje cell layer (Fig. 1B). There was sparing of the cerebellar nodulus and flocculus, with intact Purkinje and granular cell layers without evidence of severe gliosis (Fig. 1C, D). Deep cerebellar nuclei were present but contained large inclusions. Medial deep nuclei appeared to be more severely distorted with inclusions than the dentate nucleus.

Inclusions and gliosis were present throughout the brainstem. The abducens nucleus appeared normal and there appeared to be cells with PAV-positivity in the abducens nucleus. Putative EBNs with small inclusions were identified in the para-median pontine reticular formation (PPRF) in the dorsal pons just rostral to the abducens nucleus on account of their medium-size and PAV-positivity. Putative IBNs (medium-sized) were identified caudal and medial to the abducens nucleus and appeared fairly intact despite small inclusions. PAV staining was very light in the IBN region and few PAV-positive cells were identified; however, functional synapses with synaptophysin staining were present on the neurons. Putative-OPNs were found, but the sample did not contain the complete OPN region so that generalized statements on the OPN population are not possible. Neurons in the OPN vicinity and medial pons contained massive inclusions (Fig. 2A–D) and were more severely affected than deep cerebellar nuclei, in general. The OPN region did not stain for PAV or glycine transporter. The inferior olive and the medial vestibular nuclei appeared normal and the inferior olive stained strongly positive for synaptophysin.

Discussion

The most striking finding was the nearly complete absence of Purkinje cells in the dorsal cerebellar vermis (Fig. 1A, B). As Purkinje cells normally inhibit the FN, their absence suggests that FN is dysregulated. This may cause the cerebellar choke signal on the IBNs to activate prematurely, resulting in intrasaccadic decelerations. Within the brainstem, diffuse neuronal inclusions were seen. As expected, given normal initial velocity of LOTS saccades, EBNs and the abducens nucleus appeared relatively intact with minimal inclusions. Neuronal loss and extensive neuronal inclusions were clearly evident around the pontine raphe (Fig. 2A–D). This, in combination with the lack of staining to PAV and glycine transporter in the OPN region and the presence of degenerating cells nearby, suggests that the OPN region (and possibly the latch circuit, if it is located nearby) is abnormal and may contribute to saccadic interruption, although normal putative-OPN neurons could be found. PAV staining is associated with cells with high oxidative metabolism and fast-firing neurons, including EBNs, IBNs, and OPNs (Celio, 1990; Horn et al., 1995). Brainstem staining was light, raising the possibility of artifactual minimization due to long-standing formalin pre-fixation of the tissue. However, light PAV staining was identified in the IBN area, but not in the OPN area. In addition, the

IBN area stained for synaptophysin. Synaptophysin staining was negative in the OPN, but the reason for this is unclear.

These anatomic results raise an interesting question regarding the correlation between neuronal structure and function. What proportion of a neuronal population must be lost before behavioural changes become manifest? Inclusions were seen in many brainstem neuronal populations but some of these appear to function normally, such as the EBNs, and LOTS patients have a paucity of clinical brainstem involvement. However, it is reasonable to conclude that the more extensive the inclusions, the less well the cell population functions. The most extensive inclusions were seen close to the OPN-area in the pons.

Pathologic findings suggest that interrupted saccades in LOTS may be caused by premature OPN re-activation and/or inappropriate firing of IBNs. Microstimulation in the OPN area mid-saccade in monkeys leads to interrupted saccades similar to those in LOTS (Keller et al., 1996), suggesting that premature OPN re-activation may be responsible. However, cerebellar clinical dysfunction, lack of saccadic slowing, and significant loss of cerebellar cells, suggest that inappropriate IBN firing is more likely.

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Fig. 1.

Cerebellar vermis photomicrographs. (A) Luxol stain through vermis lobules reveals a nearly complete loss of Purkinje cells (one visible at arrow) and atrophy of the granular cell layer. (B) Holzer stain through vermis lobules reveals a thick area of violet staining, consistent with granular cell layer and white matter gliosis. (C) Luxol stain through the nodulus with preservation of Purkinje cells (arrow) and granular cell layer. (D) Holzer stain through the nodulus appears normal without gliosis. (See Color Plate 6.11.1 in color plate section.)

Fig. 2.

(A) Drawing of a transverse caudal pontine section demonstrating the region of the nucleus raphe interpositus (RIP) (box), containing OPNs shown in B—D. MLF, medial longitudinal fasciculus; 7n, seventh nerve; NRPC, nucleus reticularis pontis caudalis; ml, medial lemniscus; PN, pontine nuclei; Mo5, trigeminal motor nucleus; RtTg, reticulotegmental pontine nucleus. (B) Low-power photomicrograph of the Luxol-stained RIP (box in A). Hatched line is pontine midline, with OPNs just off the midline (black arrows). (C and D) High-powered photomicrographs of Luxol-stained OPNs with massive inclusions. (See Color Plate 6.11.2 in color plate section.)