Aberrant regeneration of the oculomotor nerve: implications for neurosurgeons

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Aberrant regeneration of cranial nerve III, otherwise known as oculomotor synkinesis, is an uncommon but well-described phenomenon most frequently resulting from trauma, tumors, and aneurysms. Its appearance usually follows an oculomotor palsy, but it can also occur primarily without any preceding nerve dysfunction. It is vital that neurosurgeons recognize this disorder because it may be the only sign of an underlying cavernous tumor or PCoA aneurysm. The tumor most often implicated is a cavernous or parasellar meningioma, but any tumor that causes compression or disruption along the course of the oculomotor nerve may cause primary or secondary misdirection. The most common clinical signs of oculomotor synkinesis consist of elevation of the upper eyelid on attempted downward gaze or adduction, adduction of the eye on attempted upward or downward gaze, and constriction of the pupil on attempted adduction. The authors present the largest series of patients with oculomotor synkinesis, including those in whom it developed after neurosurgical intervention, to illustrate various presentations. In addition, the various mechanisms that contribute to synkinesis are reviewed. Last, the treatment strategies for both oculomotor palsies and synkinesis are discussed. (DOI: 10.3171/FOC-07/11/E14)

KEY WORDS • aberrant regeneration • Faden operation • oculomotor nerve • palsy • synkinesis

Cranial nerve palsies are a common neuroophthalmic manifestation of disease involving the cavernous sinus, brainstem, and skull base. Patients with oculomotor nerve dysfunction usually present with a combination of ptosis, problems with adduction, elevation, depression, and variable mydriasis. Often CN III dysfunction may improve spontaneously, but occasionally the nerve fails to recover completely. In a subset of these patients with persistent partial CN III dysfunction, apparent co-firing of muscles innervated by the oculomotor nerve suggests synkinetic miswiring. This process has been referred to as aberrant regeneration. Aberrant regeneration of the oculomotor nerve has been a perplexing issue over the past century. As early as 1879, the phenomenon of lid retraction with downward gaze or adduction, which would later be termed the “pseudo von-Graefe” sign, was reported in the literature in association with recovery of the CN III. There was some confusion as to what was causing the lid retraction. Theories ranged from proposed oculomotor nucleus involvement to suggestions that the frontalis muscle was responsible. Parallels to regeneration of the facial nerve were also drawn when synkinesis of the seventh cranial nerve was studied in greater detail, probably because it manifests with more obvious signs for both patients and their physicians.

Scientific evidence to support the idea of regenerating fibers as a peripheral process came from Ramon y Cajal in 1928 when he severed the sciatic nerve of a cat and found that the fibers originating from the proximal end of its 2 trunks demonstrated haphazard regrowth without concern for their original pathways. In 1935, Bielschowsky confirmed the anatomy when he stated “in the course of healing, some of the nerve fibers which proceed from the central part of the trunk of the third nerve do not find their original sheaths in the peripheral part of the nerve but go astray, so that they arrive at muscles to which they do not belong. It seems that the nerve fibers in the course of healing prefer certain ‘routes’ for growing in the wrong sheaths, so that in the majority of cases the impulse to look down and in produces the strongest contraction of the levator of the upper lid.” Alternatively, there may not be preferential growth toward a given sheath, but rather the additional innervation to the levator is not appreciated in upward gaze because the eyelids are already open.

Abbreviations used in this paper: CN = cranial nerve; PCoA = posterior communicating artery.
Further groundbreaking work was published by Bender and Fulton in 1939 when they cut the CN III in experimental monkeys. First, they observed regeneration that was notable for vertical restriction and lid retraction on downward gaze that is now accepted as part of oculomotor synkinesis. In addition, they also proved that some of the vertical limitation was due to relative restriction (cocontraction of the superior and inferior rectus) by severing selectively the superior or inferior rectus muscles; this resulted in an increased vertical movement in a direction opposite the severed muscle, indicating that the vertical limitation was restrictive rather than residual paresis.\textsuperscript{2,3,21}

Oculomotor nerve injury (as with other CN palsies) may be categorized into 3 different degrees.\textsuperscript{16} First-degree injuries, or conduction block, are those in which the continuity of the axon is maintained. In this setting, full function returns once the block is removed. Such endoneurial continuity has been histopathologically confirmed in microvascular palsies,\textsuperscript{1} often occurring in patients with diabetes, hypertension, or other vascular disease. This anatomical continuity offers a good explanation for why aberrancy rarely if ever occurs after an ischemic oculomotor nerve insult. Sunderland further supported this idea with his work that suggested that an intact endoneurium prevented misdirection. Second-degree injuries, or crush injuries, result in disruption of the axon, while the endonurial tubes are preserved. Although there is wallerian degeneration distal to the injury site, as the nerve regenerates it is confined to its original architecture, and aberrant regeneration generally does not occur. Third-degree injuries, however, are those in which the nerve and endoneurium are disrupted. As the nerve regenerates, it may create an aberrant pathway as it attempts to bridge the severed endoneurium.

Synkinesis can manifest after a wide array of insults to the oculomotor nerve. The classic presentation is after rupture of an intracranial aneurysm, commonly of the PCoA. Most of these develop acutely following aneurysmal rupture and therefore are often first seen by neurosurgeons. In addition, it can also be seen following trauma, development of mass lesions, and, rarely, ischemia. Surgery-induced trauma is also a reported cause, and aberrant regeneration following neurosurgical manipulation in or around the cavernous sinus can be a major symptomatic complication of that surgery (SA Newman, unpublished data). Unfortunately, it can be missed under those circumstances because surgical success is based on patient survival and tumor resection, and minor morbidities such as synkinesis are generally overlooked or ignored, especially if the patient is never seen by an ophthalmologist. While the lid retraction with downward gaze and adduction is seldom more than a minor cosmetic disorder, the occurrence of cocontraction of the superior and inferior rectus muscles produces permanent limitation in vertical gaze and thus symptomatic diplopia that may be very resistant to surgical correction.

Aberrant regeneration following an aneurysm- or surgery-induced CN III palsy is probably more common than is currently recognized. Although lid retraction can be easy to recognize if a patient is asked to look in all nine positions of cardinal gaze, it can also be missed easily if the clinician is not looking for it and if the patient does not bring it to their attention. Other forms of synkinesis are more difficult to appreciate, namely cocontraction of the vertical rectus muscles. This can be mistaken for incomplete resolution of CN III palsy unless there is significant globe retraction or the intraocular pressure is checked in vertical gaze to confirm a restrictive process.

Despite the classic teaching that aberrant regeneration will not occur following diabetic ischemic oculomotor paresis, it has been reported. In 1957 Walsh reported 4 cases,\textsuperscript{7,25} and it has even been reported on the contralateral side of a lesion\textsuperscript{9} or following an ischemic insult.\textsuperscript{13} These are both highly unusual situations surrounding the appearance of synkinesis. If it presents under these circumstances, even in the setting of highly suspected ischemia, additional neuroimaging is warranted. In the absence of a traumatic origin, a parasellar lesion must be presumed and further study is warranted.

There are some patients in whom CN III palsy never develops prior to synkinesis. In this situation, it is considered primary aberrant regeneration because there is no preceding palsy. This has rarely been reported with migrainous ophthalmoplegia,\textsuperscript{5,11} but it is most commonly seen in patients with parasellar/cavernous sinus meningiomas and cavernous sinus aneurysms.\textsuperscript{17,24} There have also been reported cases related to PCoA aneurysms.\textsuperscript{12} One such example of a PCoA aneurysm causing primary aberrancy was described by Cox and colleagues,\textsuperscript{19} who argued that aneurysms at or near the cavernous sinus should be considered in the differential diagnosis whenever an elderly patient presents with ophthalmoplegia and signs of aberrancy, especially lid elevation on downward gaze. These cases bring into question the concept of misdirection down a previously disrupted tract because the CN III in these patients was never grossly disrupted. An alternative theory, ephaptic neuronal transmission, has been suggested.

Ephaptic transmission differs from traditional neuronal transmission in that it is the propagation of messages directly between axons instead of at the synapse. This is thought to occur as a slow-growing lesion, such as a meningioma, allows subclinical destruction and concomitant regeneration of CN III fibers. This in turn may allow for electrical cross talk between individual fibers of the CN III, especially if their myelin sheaths have been damaged by the slow compression. This has been a somewhat controversial mechanism, however, with the authors of numerous experimental models arguing both sides of this debate.\textsuperscript{18,20–23} Furthermore, although this concept has been proven in animal models, it has not been identified in the human oculomotor nerve, and, as such, its role in synkinesis is uncertain.

\section*{Clinical Material and Methods}

Following approval for a retrospective study by the institutional review board at the University of Virginia Health System, clinic charts of patients treated from January 1, 1981, to July 31, 2007, were retrospectively reviewed for the diagnosis code of aberrant regeneration involving the oculomotor nerve. There were a total of 56 patient records found. Each patient had been fully evaluated by the same neuroophthalmologist (S.A.N.). Additional data obtained from outside institutions as part of the clinical care of these patients were included in the analysis. The variables studied included patient age at initial presentation, initial diagnosis or cause of CN III palsy, neurosurgical interventions performed before and after the onset of aberrant regenera-
Aberrant regeneration of the oculomotor nerve results in the discovery of oculomotor misdirection, initial signs of the misdirection, any ocular interventions performed to improve binocularity or ptosis, and initial and final visual acuity.

Results

Of the 56 records reviewed, 2 were excluded because the data were incomplete or the diagnosis of aberrant regeneration was uncertain. Of the remaining 54 patients, 15 were male and 39 were female. The leading primary diagnosis was trauma. Twenty-five patients suffered a traumatic CN III palsy, in 14 patients the cause was related to a tumor, and in 8 the cause was related to an aneurysm. The most common tumor was a meningioma (8 patients); 3 patients harbored a pituitary adenoma, the second most common tumor. There was 1 case of congenital oculomotor palsy, 1 associated with zoster ophthalmicus and complete ophthalmo-mygia, and 2 in which the origin was unclear despite multiple workups.

The time to discovery of oculomotor misdirection varied dramatically, and ranged from 36 days to >39 years. This was due in part to the fact that not all patients were followed up by an ophthalmologist, and most patients who presented with signs of aberrancy at their initial neuroophthalmologic visit were more than 1 year from discovery of their initial lesion. Of the patients in whom evaluation was performed by an ophthalmologist within 6 months of their initial injury or surgery, the mean time to the first appearance of aberrant regeneration was 116 days (11 patients). If the patients were seen between 6 months and 1 year after their initial presentation (mean 247 days), they all had early signs of aberrant regeneration, even if the diagnosis was not made at that time (19 patients). The mean age at the time of initial presentation of the cranial nerve palsy was 42 years (range 1 day–89 years). Eleven patients (20%) presented initially with additional CN deficits, the most common being a CN VI palsy and the most dangerous being a CN V-1 palsy and with 2 of 4 patients developing vision-threatening neurotrophic corneal ulcers.

The most common presenting sign was vertical motility restriction. Forty-nine patients (91%) had significant vertical restriction at the onset of their misdirection syndrome. In 2 of these patients, intraocular pressure was measured and documented in upward gaze; an increase in pressure was noted in the affected eye as the patient attempted to look up. Lid retraction was noted in 46 patients (85%), although this sign was often detected after the discovery of vertical restriction. Thirty-five patients (65%) had persistent diplopia, and of these 15 (43%) opted to undergo extraocular muscle surgery, and 6 of these also requiring ptosis correction. Three of those patients (20%) required a second muscle procedure to further improve their extraocular motility, and 2 (33%) required a second procedure to further improve their ptosis or upper-eyelid contour. This high reoperative rate for ptosis surgery may reflect the fact that lid height is less predictable with the aberrant fibers innervating the upper lid, and the surgery usually aims to undercorrect the lid height in these cases to prevent excessive lagophthalmos. Table 1 provides a summary of our results.

Table 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age at presentation</td>
<td>42 yrs</td>
</tr>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>15 (28)</td>
</tr>
<tr>
<td>female</td>
<td>39 (72)</td>
</tr>
<tr>
<td>cause</td>
<td></td>
</tr>
<tr>
<td>trauma</td>
<td>25 (46)</td>
</tr>
<tr>
<td>tumor</td>
<td>14 (26)</td>
</tr>
<tr>
<td>aneurysm</td>
<td>8 (15)</td>
</tr>
<tr>
<td>hemorrhage</td>
<td>3 (6)</td>
</tr>
<tr>
<td>congenital</td>
<td>1 (2)</td>
</tr>
<tr>
<td>unknown/other</td>
<td>3 (6)</td>
</tr>
<tr>
<td>neurosurgical intervention</td>
<td>25 (46)</td>
</tr>
<tr>
<td>no. of days to presentation of AR seen</td>
<td>116 days†</td>
</tr>
<tr>
<td>w/in 6 mos of primary diagnosis</td>
<td></td>
</tr>
<tr>
<td>no. w/ additional CN deficits</td>
<td>11 (20)</td>
</tr>
<tr>
<td>CN II (NLP vision)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>CN IV</td>
<td>4 (7)</td>
</tr>
<tr>
<td>CN V</td>
<td>4 (7)</td>
</tr>
<tr>
<td>CN VI</td>
<td>6 (11)</td>
</tr>
<tr>
<td>CN VII</td>
<td>1 (2)</td>
</tr>
<tr>
<td>motility or ptosis op</td>
<td>15 (28)</td>
</tr>
<tr>
<td>signs of misdirection</td>
<td></td>
</tr>
<tr>
<td>VR</td>
<td>49 (91)</td>
</tr>
<tr>
<td>lid elevation or hang up w/ downgaze &amp;/or adduction</td>
<td>46 (85)</td>
</tr>
<tr>
<td>miosis w/ adduction, depression, or elevation</td>
<td>9 (17)</td>
</tr>
</tbody>
</table>

* AR = aberrant regeneration; NLP = no light perception; VR= vertical restriction.
† For 11 patients.

Illustrative Case

This 21-year-old right-handed woman was referred for persistent diplopia following a motor vehicle accident 2 years earlier. She had been followed up by an ophthalmologist since the accident and at her last examination was noted to have some return of CN III function without evidence of aberrant regeneration. On examination at our clinic, she exhibited limited elevation of the right eye and attempt at adduction caused a slight elevation of the right eyelid. Her intraocular pressure was recorded in straight gaze and found to be 13 mm Hg; when she attempted to elevate the right eye the pressure rose to 20 mm Hg, confirming cocontraction and therefore aberrant regeneration. Once she was found to have stable misalignment of her eyes, she underwent a “recession” of her right lateral rectus muscle and resection of her right medial rectus to correct her exodeviation. In addition, the tendons of the 2 muscles were placed 1-tendon-width lower on the globe in an attempt to improve her right hypertropia. Postoperatively she had an excellent cosmetic result with a normal appearance in straight-ahead gaze, but she had persistent diplopia secondary to the extreme limitation of vertical movement of the right eye and her small area of binocularity.

Discussion

Unfortunately, it may not be possible to determine the exact percentage of patients with CN III palsy in whom misdirection subsequently develops. This is due in part to the fact that patients in whom CN III function is recovered without significant synkinesis may never present to an oph-
thalmologist for further evaluation, and therefore a selection bias would be created in any retrospective study. It is also clear that without detailed quantitative motility analysis by a neuroophthalmologist, subtle cases of aberrant regeneration are commonly overlooked. What is clear from the cases presented in this series, however, is that there are several predominant factors that seem present in the patients in whom misdirection develops: 1) a history of trauma, 2) the presence of parasellar and cavernous tumors such as meningiomas, and 3) previous surgical manipulation.

Currently, there is not much that can be done to prevent synkinesis; the key is to recognize it so that patients can be appropriately referred for subspecialty management. Even in the absence of misdirection, referral of patients with persistent motility deficits is warranted because of the potential for intervention and subsequent improvement in their quality of life. In addition, awareness of this phenomenon allows for more thorough preoperative counseling of neurosurgical patients.

Perhaps the most interesting findings of this review were the frequency with which vertical restriction occurs with aberrant regeneration and that it is often the first sign. It is also a very subtle finding in its early presentation, and without careful ophthalmological examination it can be easily missed or confused with failure of CN III recovery. The images in Fig. 1 demonstrate that without careful examination in all nine positions of cardinal gaze a patient can appear normal in primary gaze. Because cocontraction producing restriction is at fault here, checking intraocular pressure may be essential to establishing the diagnosis. In addition, detection of other CN palsies with appropriate referral is essential to their proper management, especially in patients with parasellar and cavernous sinus lesions in whom a trigeminal palsy can result in neurotrophic changes, as was demonstrated in two of our patients in whom corneal ulcers developed.

The treatment strategies are quite varied depending on the unique clinical manifestations in each patient. In addition, the goals and expectations of the patient must be considered. There are two primary objectives for these patients. First, ocular alignment with useful binocularity in primary position and downward reading gaze allows patients to perform most activities without being forced to hold their head in a strange position or use a patch. This is most critical for children, who can develop torticollis, abnormal facial structures, and amblyopia if not corrected early. The second objective is cosmesis, namely the correction of ptosis and ocular misalignment, so that patients can regain a normal appearance.

Fig. 1. This patient presented with a headache and a CN III palsy and was found to have subarachnoid hemorrhage and a left PCoA aneurysm. Two months after placement of an aneurysm clip, her ptosis improved and she began to notice double vision. She was eventually referred to a neuroophthalmologist for persistent issues with diplopia and was found to have aberrant regeneration causing significant vertical restriction. Notice here that as she looks up or down, the left eye moves far less than the right. Also notice how the left eyelid elevates in downward gaze. The binocular single-vision (BSV) field on the bottom left demonstrates how the patient develops diplopia in up or downward gaze.
With oculomotor synkinesis it can be difficult to achieve both of the aforementioned goals, and sometimes one must be sacrificed for the other. Because of the severe limitation in vertical movement that patients can experience, there will be a very limited area where fusion can occur and diplopia avoided. Furthermore, the surgical correction can be unpredictable, and therefore it may be difficult, if not impossible, to get the eyes aligned in primary position. Under these circumstances, patients may prefer to have some subtle ptosis to hide their diplopia. Alternatively, some patients would rather live with the double vision and have a “normal” appearance with eyelids at equal heights.

Prior to surgical correction, an attempt to align the eyes using botulinum toxin can be useful or at least informative. By injecting the nonparetic lateral rectus, you may be able to weaken the muscle enough to reduce the patient’s head turn. Unfortunately this effect will not last forever, but it may offer a preview of how a patient will respond to a lateral rectus recession. The other advantage of using botulinum toxin is that it reduces the potential contracture that will occur in the unopposed lateral rectus. Unfortunately, botulinum toxin is less likely to be useful in dealing with vertical diplopia and the limitation in upward and downward gaze.

There are a few surgical techniques that can be useful in treating oculomotor paresis and misdirection. The first is known as the Faden operation or, more appropriately, a posterior fixation suture. This procedure aims to limit the

**Fig. 2.** A: Neuroimage obtained in a patient who underwent a pterional craniotomy for a cavernous sinus–clivus meningioma and postoperatively developed a CN III palsy with subsequent oculomotor synkinesis. She underwent a left-sided inferior rectus recession with Faden suture. B: The patient looking in the nine cardinal gaze directions exhibits severe limitation of vertical movements in the right eye and right upper lid elevation when she attempts to look down. C: Hess screen representing the patient prior to the Faden procedure, which demonstrates limitation of vertical gaze on the right and secondary overaction on the unaffected side, so much so that the vertical movements were off the page. D: Postoperative Hess screen now demonstrating limitation of infraduction on the left eye. Note how the bottom lines on each side are closer together. E: Preoperative binocular single-vision field, demonstrating the small island centrally where the patient can see without diplopia, but develops it as soon as she attempts to look down. F: Postoperative binocular field has a larger central area of single vision, especially in downward gaze. Postoperatively, she was able to read without diplopia.
range of the nonparetic eye in a particular gaze of action by changing the arc of contact of a given extraocular muscle. Although it may seem counterintuitive to operate on the uninvolved eye, and patients may have questions regarding its use, it is a very effective option in that it causes equal restriction of both eyes. This is particularly useful when there is vertical restriction as a result of aberrancy; as a patient attempts to look down, to read for instance, the nonparetic eye will travel farther and cause diplopia. If you limit that eye in downward gaze by placing a Faden suture on that eye’s inferior rectus, then neither eye will be able to depress well, and the patient will have less diplopia when looking down. This can be best demonstrated by the use of binocular single-vision fields. The Faden operation is one of the few methods of expanding the area of binocularity. Binocular single-vision fields also demonstrate that the Faden suture will not only shift the area of binocularity to primary and the down-gazing reading position but will paradoxically enlarge the area of single vision, despite the restriction that it causes on the nonparalytic eye. The images in Fig. 2 demonstrate the results obtained in a patient who underwent a Faden procedure.

There are other procedures available that attempt to put the area of binocular single vision in a more useful location for the patient. Because of the significant vertical restriction, these patients will never be able to move their eyes in tandem, especially vertically. If they can be aligned in primary position and/or in a reading position, however, then the patient will generally be satisfied. One patient in our study had to maintain an awkward chin-down head-tilt position to see singly and ultimately developed arthritis in her neck.

Several of our patients underwent one or more of the aforementioned procedures for eye realignment. One type of procedure is referred to as a recess–resect procedure, in which the medial rectus muscle is made shorter and tighter, while the lateral rectus is recessed further back on the globe to weaken it. This procedure allows the eye to adduct more effectively, because most patients with a persistent CN III palsy are exotropic. Muscle surgery is often conducted with adjustable sutures, thus maximizing the chance of alignment in desired positions. Unfortunately, due to the aberrant signals reaching those muscles, no amount of strengthening or weakening will stop their co-contraction; the best that we can hope for is an orthophoric appearance and bringing the affected eye’s small range of movement into the patient’s area of central vision.

Conclusions

Aberrant regeneration of the CN III following surgical intervention is likely more common than current literature would suggest. Although it is briefly mentioned in neurosurgical texts in association with slowly progressive cavernous sinus masses, the persistent symptoms of misdirection are not discussed. Instead, the vertical motility disturbances that it causes are probably misinterpreted by most surgeons as an incomplete recovery of the patient’s CN III palsy. It is one of the leading postoperative ophthalmological morbidities following cavernous sinus surgery. It is also a common complication of aneurysmal hemorrhage and subsequent surgery. Although surgical intervention for life-threatening or disabling cranial tumors or aneurysms should not be avoided because of the potentially increased risk of postoperative oculomotor synkinesis, neurosurgeons should be aware of its existence and its clinical manifestations. Based on our findings, any patient with a new oculomotor nerve paralysis should undergo a full ophthalmological examination to quantify ocular motility and to determine the presence of other occult comorbidities, including trigeminal and other ocular motor dysfunction. With a better understanding of this entity, surgeons can be more sensitive to the symptoms of diplopia and lid positioning that may be apparent at presentation. Finally, surgeons should realize that potential treatment strategies exist for some patients and therefore they need to recognize this condition early to refer their patients for evaluation and possible treatment.

References

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