Divergence Insufficiency Revisited

Natural History of Idiopathic Cases and Neurologic Associations

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Objectives: To determine the natural history of primary divergence insufficiency and to identify clinical features that distinguish patients with this neurologically isolated form of divergence insufficiency from those harboring neurologic disorders.

Methods: Retrospective survey of patients with divergence insufficiency. Patients were categorized into 2 groups, primary (ie, neurologically isolated based on clinical criteria) and secondary (ie, associated with a neurologic or systemic disorder). Long-term follow-up and clinical features of the 2 groups were compared.

Results: Of the 20 patients with primary divergence insufficiency, 19 (95%) were older than 50 years. Symptoms resolved in 8 (40%) of 20 patients after a median of 5 months. None of these patients developed signs of an underlying neurologic disorder during follow-up. Of the 15 patients with secondary divergence insufficiency, an underlying neurologic or systemic disorder was either known or initially suspected in all based on the initial history and physical examination. Divergence fusion amplitudes were significantly larger in patients with secondary divergence insufficiency compared with those with primary divergence insufficiency, although there was considerable overlap of values between the 2 groups.

Conclusions: Primary divergence insufficiency is generally a benign condition. Many affected patients experience spontaneous resolution of double vision within several months. The clinical neurologic evaluation is a powerful tool that distinguishes those with a primary disorder from those harboring an underlying neurologic or systemic condition. It is reasonable to initially defer further investigation, including neuroimaging, in patients who have no other neurologic symptoms or signs.


DIVERGENCE insufficiency refers to a clinically defined acquired disorder of ocular horizontal version, characterized by full-appearing ocular ductions and comitant esotropia at distance. An affected patient experiences double vision when viewing distant objects, but not when viewing objects up close. Although it has been described for more than a century, divergence insufficiency remains a controversial entity. For example, many investigators propose criteria to differentiate divergence insufficiency from divergence paralysis or paresis. However these arbitrarily defined criteria more likely describe varying severity of symptoms and ocular motor signs along a continuum of the same condition. Since true paralysis of divergence generally cannot be documented in most affected patients, I prefer the term divergence insufficiency to describe this disorder, regardless of the severity of associated symptoms and signs.

Another area of controversy concerns whether divergence insufficiency is a localizing sign referable to injury of a “divergence center,” or is a nonlocalizing sign associated with a variety of focal and diffuse brain insults. Since divergence is an active process, not a passive one associated with relaxation of the medial rectus muscles, some investigators hypothesize that a “divergence center” must exist. This concept was first championed by Bruce, whose reasoning for its existence was admittedly “guided by deduction rather than influenced by definite proof.” In support of that hypothesis, some investigators have reported clinical-radiographic and clinical-pathologic correlations of patients with divergence insufficiency associated with focal lesions, usually of the pons and mid-brain, but also in other locations, such as the craniovertebral junction. On the other hand, patients with divergence insufficiency and a variety of diffuse brain injuries have also been described. The
PATIENTS AND METHODS

I reviewed the medical records of patients with divergence insufficiency that I had evaluated from July 1987 through April 1999 in my neuro-ophthalmology practice at a single institution. My practice represents a balance of primary care and referral-based consultative neuro-ophthalmology. Patients in the study population shared the following symptoms: double vision when viewing distant objects, full-appearing ocular ductions, and esotropia identified during cover testing while fixing a distant target. In addition, all patients underwent examination of ocular motility using a Maddox rod to demonstrate that the angle of uncrossed deviation increased as the viewing distance increased, remained the same or decreased in right and left gazes at distance, and decreased as the viewing distance decreased. All patients with double vision routinely were assessed for the speed of saccades and for the presence of nystagmus to identify signs of abducens nerve palsy or internuclear ophthalmoplegia. No such signs were identified in any of the patients in this series. All patients had undergone a general neurologic examination by a board-certified neurologist (D.M.J.).

The following information was abstracted from the medical records: current medical history, past medical history, details of the ocular motor and general neurologic examinations, results of radiographic and laboratory tests, and long-term follow-up of those cases that were classified as idiopathic. Since the cardinal symptom of divergence insufficiency is double vision, this symptom was used to establish the total duration of the follow-up. This period included the duration of diplopia prior to the first evaluation in addition to the duration of diplopia until either resolution of it or until the last follow-up evaluation. Information obtained from direct telephone interviews with the patients and review of office records of referring physicians who continued to follow up some patients were included in the determination of follow-up.

Divergence fusion amplitude had been measured in most patients by first neutralizing their distance esotropia using a handheld loose prism. Then, a horizontal prism bar was used to place increasing strengths of base-in prism over the other eye until fusion could no longer be maintained, as assessed subjectively using a distant target for fixation. A Maddox rod was also used to determine the near point of orthophoria in most patients.

Each patient was classified into 1 of 2 categories of divergence insufficiency based on results of the general neurologic assessment at their initial evaluation. Patients with primary divergence insufficiency were those who had no other neurologic symptoms or signs, and patients with secondary divergence insufficiency were those who had additional symptoms or signs of neurologic dysfunction. The results of CT or magnetic resonance imaging (MRI), available at the time of initial evaluation, were not initially considered since one of the aims of this study was to identify clinical features that might be helpful in predicting which patient was harboring a neurologic disorder.

There were 20 patients classified as having primary and 15 patients classified as having secondary divergence insufficiency. Of the 20 patients with primary divergence insufficiency, there were 10 women and 10 men, ranging in age from 24 to 90 years, with a median (mean) age of 74 (70) years. All but 1 patient were older than 50 years. Of the 15 patients with secondary divergence insufficiency, there were 11 women and 4 men, ranging in age from 8 to 86 years, with a median (mean) age of 56 (51) years. Using the Mann-Whitney test, there was no significant difference in the size of esotropia in forward gaze at distance or near point of fusion between the groups of patients with primary and secondary divergence insufficiency (Table 1). While the size of divergence fusion amplitude was significantly larger in the group of patients with secondary disorders than in the primary group, the magnitude of this difference was small and the range of values between the 2 groups demonstrated considerable overlap (Table 1).

All patients with primary divergence insufficiency had been specifically asked whether their double vision was preceded by a specific event. Eight (40%) of the 20 patients recalled such an event, including a viral prodrome in 3 patients, minor head trauma in 2 patients, and hospitalization for an unrelated illness in 3 patients. On the other hand, it remains possible that these events were casual and not pathogenetically important.
The radiographic and laboratory evaluation of the 20 patients with primary divergence insufficiency did not reveal any unsuspected disorders. Six patients underwent CT and 10 underwent MRI. These studies were unrevealing in all patients. While none of the patients had other symptoms to suggest giant cell arteritis or myasthenia gravis, erythrocyte sedimentation rate (performed in 7 patients) and acetylcholine receptor antibody assay (performed in 6 patients) were tested, and the results were normal in all. Intravenous edrophonium chloride testing was performed in 2 patients because of the referring physician’s concern about the possibility of myasthenia gravis despite the absence of other symptoms or signs of this condition, but the test did not resolve double vision or reduce the amount of esotropia.

Three patients with primary divergence insufficiency continued to have esotropia at the time of their last evaluation, although 2 had shown improvement. They had experienced double vision for 5 weeks, 5 months, and 6 months, respectively, up to the time of their last evaluation, but did not return for further follow-up. When their medical records were reviewed at the time this study was being designed, I learned that they had since died of unrelated illnesses, so the course of their disorder could not be completely ascertained. In the remaining 17 patients who were still alive, the total duration of follow-up extended from 1 month to 16 years (median, 35 months). Only 2 patients were followed up for less than 6 months. One patient was followed up for only 1 month, but her esotropia resolved during that time. The other patient was followed up for 5.5 months, and his esotropia resolved during the first month of that period. During the total period of follow-up, none of the patients developed an alternative neurologic disorder.

In the 17 patients with primary divergence insufficiency who had adequate information to ascertain long-term follow-up, double vision persisted in 9 individuals. None of these patients underwent strabismus surgery. Their symptom was controlled using prisms. The duration of time to resolution of double vision in the remaining 8 patients was 1 week to 26 months (median, 5 months). It is possible that with longer follow-up, the number of patients with resolution of diplopia might increase.

The disorders associated with the 15 patients with secondary divergence insufficiency are listed in Table 2. Many of these patients had an established underlying disorder (eg, cerebellar degeneration) and were referred because of double vision. Other patients without known neurologic disorder (eg, midbrain metastasis) were referred to evaluate double vision. Regardless of whether their underlying responsible disorder was established or not, additional neurologic symptoms and signs were readily apparent in all of these patients. In those patients without an established disorder, additional clinical clues indicated the need for neuroimaging or additional diagnostic studies, independent of the signs of divergence insufficiency.

Signs typical of divergence insufficiency were identified in 9 patients without intracranial hypertension (Table 2), including 2 with temporal arteritis. One of these patients had posterior ischemic optic neuropathy, but no other signs of orbital ischemia. No signs of orbital ischemia were present in the second patient. Esotropia resolved within days of initiating corticosteroid treatment in both patients. The patient with a metastatic lesion of the midbrain additionally had skew deviation, an afferent pupillary defect without visual loss, and other signs of brainstem injury, but no symptoms or signs of intracranial hypertension. Magnetic resonance imaging did not identify hydrocephalus or involvement of the lesion along the anatomic course of the abducens nerve. The other patient with focal brainstem injury, a stroke with double vision, vertigo, and left arm numbness, did not have the responsible lesion identified by the CT.

The remaining 6 patients with secondary divergence insufficiency had symptoms and obvious signs of intracranial hypertension (eg, papilledema) (Table 2). Only 1 of these patients, the one with a frontal lobe tumor, had a focal lesion.
longed period of time to determine whether the esotropia might resolve spontaneously. In the meantime, temporary paste-on and, if stable for several weeks, permanent ground-in prisms, were effective and conservative means of relieving symptoms in these patients.

No unsuspected CT or MRI abnormality was identified in those patients whose only presenting neurologic symptom and sign was double vision and divergence insufficiency. None of the patients initially classified as having primary divergence insufficiency developed additional neurologic dysfunction during the period of follow-up. Neuroimaging was not performed in 4 of these patients so it is possible that some of them had unsuspected lesions. However, it seems unlikely, since divergence insufficiency resolved in all 4 patients and no other neurologic problems developed during the time of each patient’s follow-up of 1 month, 5.5 months, 34 months, and 44 months, respectively. It is also possible that the 3 patients who died and did not undergo long-term follow-up had some unsuspected neurologic disorder at the time they were evaluated. Again it seems unlikely, since CTs performed in 2 patients and an MRI performed in 1 were normal, and signs of divergence insufficiency were improving in 2 of these patients at the time of their last evaluation.

In those patients with secondary divergence insufficiency, the underlying disorder was either already established or strongly suspected based on the additional neurologic symptoms and signs at their initial evaluation. With the exception of the size of vertical fusion amplitude, ocular motor signs associated with divergence insufficiency did not distinguish patients with idiopathic from those with secondary disorders. I doubt that assessment of the size of vertical fusion amplitude would be a helpful discriminating tool, however, since the size of it was small in most patients in both groups, it was measured using a subjective end point, and there was considerable overlap of values.

Instead, the initial history and physical examination proved to be powerful tools to distinguish those patients with a primary disorder from those with an underlying neurologic or systemic (ie, secondary) cause of divergence insufficiency. From a practical point of view, it seems reasonable to defer further investigation, including neuroimaging, in an affected patient who has no other neurologic or systemic symptoms or signs. Although no unsuspected neurologic disorder surfaced during the period of follow-up in these patients, I strongly recommend that a patient with isolated divergence insufficiency be followed closely to detect, for example, signs of developing intracranial hypertension or abducens nerve palsy. This recommendation is based on the small size of the study population, the problems inherent in a retrospective investigation, and the grave consequences of failing to identify other neurologic signs. This conclusion was recently confirmed by Wiggins and Baumgartner, who characterized a benign long-term prognosis in their cohort of patients with neurologically isolated divergence insufficiency.

A few comments are warranted regarding some of the disorders associated with secondary divergence insufficiency. In the 2 patients with temporal arteritis, the rapid resolution of esotropia coincident with initiation of corticosteroid treatment, along with the development of posterior ischemic optic neuropathy in 1 case, point to ischemic injury of extraocular muscles as the cause of ophthalmoparesis. Although ophthalmoplegia associated with temporal arteritis has been rarely attributed to brainstem or ocular motor nerve injury, most cases are thought to result from extraocular muscle ischemia. The association of divergence insufficiency and temporal arteritis in these 2 cases emphasizes that the diagnostic signs of this ocular motor disturbance are not localizing and could occur in other disorders associated with local injury of extraocular muscles, such as myasthenia gravis, as was identified in 1 of the patients of Lepore.

Divergence insufficiency was observed in 4 patients with pseudotumor cerebri. This association has been reported before, and has contributed to the controversy of whether divergence insufficiency represents a separate disorder or subtle sixth nerve palsy. Although the double vision reported in patients with pseudotumor cerebri is generally attributed to sixth cranial nerve palsy, I suspect that many symptomatic patients have divergence insufficiency, as suggested by Smith.

Divergence insufficiency was also observed in 2 patients, each with idiopathic cerebellar degeneration and progressive supranuclear palsy, an association that is generally not recognized in either condition. This did not cause clinical confusion, however, since divergence insufficiency was overshadowed in each patient by the cardinal signs that characterized their underlying neurologic conditions.

The diverse conditions and sites of associated lesions of the patients with secondary divergence insufficiency in this series imply that secondary divergence insufficiency is not particularly localizing, nor is it necessarily specific for intracranial hypertension. The characteristics of the patients in this series who have an idiopathic disorder suggest that if certain rules of diagnosis are obeyed, divergence insufficiency can be distinguished from sixth cranial nerve palsy in most cases using clinical techniques. Many patients were first evaluated within 1 month of the onset of symptoms, far sooner than the expected time course for the spread of comitance to convert a sixth cranial nerve palsy to a comitant esotropia. Most importantly, the esotropia remained the same or decreased in lateral gaze to either side in all patients, even those evaluated acutely. A Maddox rod was the tool used to assess ocular comitance in this study, but other methods exist, including prism-cover techniques, the Hess chart, and the Lancaster red-green test. Although each method has its advantages and disadvantages, they all suffer from being subjective. Unfortunately, since the ocular ductions appear full in a patient with suspected divergence insufficiency, objective means to assess the state of ocular comitance do not exist for office determination. Simultaneous injury of the medial longitudinal fasciculus has been postulated as another reason sixth cranial nerve palsy may appear comitant. However, none of the patients classified as primary had clinical signs of internuclear ophthalmoplegia.
These arguments do not preclude the possibility that some patients with concomitant esotropia at distance and full-appearing ocular ductions might be suffering from sixth cranial nerve palsy, not divergence insufficiency. This distinction is especially problematic in patients with other neurologic signs, most importantly those associated with intracranial hypertension. Accordingly, a patient with divergence insufficiency who has additional neurologic symptoms or signs should undergo a comprehensive neurologic evaluation that includes neuroimaging. Otherwise, neuroimaging can be deferred in patients with neurologically isolated divergence insufficiency, although careful follow-up is indicated to identify developing suspicious neurologic symptoms or signs.

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REFERENCES

tients with PG, 46% of patients with PDS, and 44% of patients with JOAG had a family history of glaucoma. There was no significant difference in the ability to taste PTC between patients with JOAG and the group of patients with PG and PDS ($\chi^2=0.4, P > 0.05$; Table). There was no difference in the ability to taste PTC between patients with PDS and those with PG ($\chi^2=0.7, P > 0.05$; Table).

The percentage of nontasters, overall and in all 3 groups (48%), is similar to the proportions found in patients with POAG in both earlier studies, a higher figure than is found in the normal population. Becker and Morton also found fewer nontasters among black patients (37%) than white patients (53%), both in those with POAG and in the normal population (17% vs 28%). Pigment dispersion syndrome is almost exclusively found in white patients, as were our participants. We found a higher prevalence of PTC nontasters among patients with either PDS or PG than did Kalmus and Lewkonia. The latter used the detection threshold (ability to discriminate between PTC and water), whereas we used the recognition threshold (ability to recognize a bitter taste), similar to Becker and Morton. However, we cannot compare our results with those of Becker and Morton because they did not examine PG as a distinct group. In summary, our data do not support the finding of a lower prevalence of PTC nontasters among patients with either PDS or PG.

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