RESPONSE: I appreciate the great efforts made by Drs. Ueno, et al., to elucidate the association of moyamoya disease with polymorphisms of the TGFβ and \( \text{TGFβR} \) genes. There are several good reasons to speculate about the association of the pathogenesis of moyamoya disease with altered gene expression of TGFβ. First, TGFβ induces neovascularization, which is typically observed in patients with moyamoya disease after surgery. Second, TGFβ increases connective tissue gene expression. Matrix-rich thickened intima is observed in patients with moyamoya disease and elastin gene expression in arterial smooth-muscle cells derived from patients with moyamoya disease is shown to be increased. Third, overexpression of the TGFβ gene in arterial endothelium in vivo causes intimal hyperplasia.

It is commonly believed by many that moyamoya vessels represent collateral channels formed as a result of stenotic change in the cerebral arterial trunks. However, there has been no evidence to support this and recently I have come to doubt this view. If moyamoya vessels represent collateral channels, it is reasonable to speculate that at an advanced stage of this disease these vessels become more abundant to compensate for reduction in blood flow caused by more severe stenotic lesions. However, the anatomic staging described by Suzuki and Kodama\(^6\) has revealed that this is not the case. In fact, dilated moyamoya vessels appear to originate from arterial trunks distal to stenotic lesions. If they are collateral channels, they should originate from arteries proximal to stenotic lesions. These facts have prompted me to speculate that moyamoya vessels may not be the result of stenotic change in the cerebral arterial trunks. Moreover, I hypothesize that the same genetic change may cause reciprocal effects, that is, arterial dilation and stenosis. If this is true, TGFβ may be the best candidate for a moyamoya disease gene because TGFβ also has reciprocal effects on vascular smooth-muscle cells; it acts as a growth inhibitor, yet it can stimulate proliferation.\(^2\) In addition, TGFβ maintains endothelium-dependent arterial relaxation,\(^4\) although it can induce intimal thickening.\(^3\)

These similarities between functions of TGFβ, and characteristics of moyamoya disease have strongly suggested an important role of TGFβ, or TGFβ signaling system in the etiology of moyamoya disease. However, Ueno, et al., demonstrated no association between moyamoya disease and polymorphisms of the TGFβ, or TGFβR, genes. Therefore, the increased expression of TGFβ, in vascular smooth-muscle cells derived from patients with moyamoya disease may not be the cause of moyamoya disease but the result of brain ischemia. They suggested three possibilities to explain the increased expression of TGFβ. I would like to add another possibility: TGFβ may be increased to preserve endothelial cell function and attenuate ischemia-induced cerebrovascular compromise.\(^1\) In summary, although not a causative factor, it is highly probably that TGFβ plays an important role in the pathogenesis of moyamoya disease.

MINORU HOSHIMARU, M.D.
Ohtsu Municipal Hospital
Ohtsu, Shiga, Japan

References


Pupils and Coma

TO THE EDITOR: I enjoyed reading the paper by Andrefsky and colleagues (Andrefsky JC, Frank JJ, Chyatte D: The clissospinal reflex in pentobarbital coma. *J Neurosurg* 90:644–646, April, 1999), who evaluated the problem of pupillary dilation and absent light reflex during pentobarbital coma. It reminded us that clinical reasoning and careful clinical examination do always have a place in caring for patients, even in the technocratic environment of neurological intensive care.

Although this study was limited to a small proportion of severely critically ill patients, the authors provided us with an important message: pupillary dilation in a patient undergoing pentobarbital coma may be a temporary phenomenon due to common painful procedures. By using an adequate (that is, intense and prolonged) light stimulus, the pupillary constriction can be obtained, thus avoiding unnecessary, risky, and costly interventions.

I would add an instructive case of a seemingly unresponsive mydriasis caused by sympathomimetic drugs. A 73-year-old woman was admitted to the coronary care unit because of acute myocardial infarct and cardiogenic shock. She was treated with very large doses of dobutamine (up to 40 mg/kg/minute to enhance contractility). Dopamine was then administered and blood pressure in-
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creased, but the patient became unresponsive, with fixed and dilated pupils. The cardiologist asked for a consultation. I observed the patient lying immobile in bed, with closed eyes and unresponsiveness to verbal stimuli. Pupils were maximally dilated and not reacting to penlight, and oculocephalic reflex was absent. In contrast with these signs, the patient was breathing quietly, grimaced to pain, and resisted passive eyelid opening. The rest of the neurological examination yielded normal results, and pupillary constriction was then demonstrated by using a powerful and sustained light stimulus. I told the cardiologist that it was conceivable that pupillary dilation was caused by sympathomimetic amines and that the patient was not in a coma, but rather in a psychogenic state of unresponsiveness. The patient then said: “You’re right, doc.”

Plum and Posner report that hypothermia and sympathomimetic drugs may cause unreactive mydriasis. Sympathomimetic drugs were also involved in two of three cases described by Larson and Muhiudeen, in which pupillary light constriction was only appreciable with an infrared pupillometer.

Alfentanil, a potent narcotic, causes a dose-dependent reduction in reflex pupillary dilation—which can be used to advantage—but maintains pupillary light constriction.1 The ciliospinal reflex is usually caused by sympathetic activation; however, barbiturate and anesthetic medications cause it by inhibiting the parasympathetic midbrain nucleus. Therefore an additive effect can be seen when barbiturate medications are used with sympathomimetic drugs, which is not an uncommon situation in patients undergoing pentobarbital coma. Hypothermia and the administration of narcotic medications can further compound the picture.

Clinicians caring for critically ill patients with neurological diseases should be aware of the complex pupillary effects of sedative agents to avoid inappropriate examinations or pessimistic prognoses.

References

RESPONSE: I would like to thank Dr. Latronico for his comments regarding the ciliospinal reflex and his personal experience.

Patients exposed to drugs that modulate the autonomic nervous system can manifest a variety of effects: some life-threatening, others benign. Anticipation of these autonomic changes, such as tachycardia or bradycardia and hypotension or hypertension, can lead to an earlier treatment response and improved patient outcomes.

To ensure good outcomes for patients undergoing difficult neurosurgical procedures, excellent postoperative care must be provided. Patients who are critically ill require careful thought and evaluation before an invasive diagnostic procedure is performed or treatment is administered. Transportation of these patients is dangerous and decision to do so should not be taken lightly.

As Dr. Latronico points out, interpretation of physical findings will always be an important part of any physician’s clinical practice. They also serve as future refinements in clinical practice, as well as incentive for research endeavors.

JOHN C. ANDREFSKY, M.D.
The Cleveland Clinic Cleveland, Ohio

Pineal Epidermoid Cysts

TO THE EDITOR: We read with great interest the article by Konovalov and colleagues (Konovalov AN, Spallone A, Pitzkhelauri DI: Pineal epidermoid cysts: diagnosis and management. J Neurosurg 91:370–374, September, 1999). They describe the clinical and radiographic features of their experience with six cases of pineal epidermoid cysts. We concur that epidermoids of the pineal body are exceedingly rare. Indeed, as noted by Dorothy Russell, the pathologist must be aware of germ cell elements coexisting with epidermoid (Case 2) and dermoid (Case 3) cysts in this region.

We note the case of a 19-year-old male in the series of Konovalov, et al. We recall a recent case at Duke University Medical Center of a 14-year-old male patient who presented with a pineal region mass, a large portion of which did not enhance on magnetic resonance images. The tumor was initially approached via ventriculoloscopy. Frozen section intraoperative consultation revealed keratinous debris. We declared our concern about the diagnosis of an epidermoid cyst based largely on the warning of Dr. Russell. We encouraged open resection, which subsequently revealed a mixed germ cell tumor consisting of mature teratoma with germinoma.

We concur with the author’s recommendation of total resection when possible, and advise that thorough pathological examination should be performed in all cases to definitively rule out the coexistence of other heterologous germ cell elements, especially in adolescent and young adult patients.

THOMAS J. CUMMINGS, M.D.
ROGER E. MCLENDON, M.D.
Duke University Medical Center Durham, North Carolina

References

RESPONSE: We appreciated the interest and wise comments of Drs. Cummings and McLendon to our paper concerning the diagnosis and management of pineal epidermoid cysts. Actually, it is the policy of the Institute "N.