The Differential Diagnosis of Fixed Dilated Pupils: A Case Report and Review

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ABSTRACT

This case report describes a patient with Guillain-Barré syndrome in whom the presence of coma and absent brain stem reflexes suggested the possibility of brainstem death. A differential diagnosis of fixed dilated pupils is presented. (**Critical Care and Resuscitation 2000; 2: 34-37**)

Key words: Pupilary abnormalities, brain stem death, Guillain-Barré syndrome

The presence of fixed dilated pupils in a comatose patient is generally considered to be an ominous sign if reversible causes of coma have been excluded. Brain death is defined according to the criteria established by the conference of the Royal Colleges and Faculties of the United Kingdom in 1976,[1] namely that all brain stem reflexes are absent:

- The pupils are fixed in diameter; no response to light.
- No corneal reflex.
- Oculovestibular reflexes absent.
- No response to painful stimulation within the cranial nerve distribution.
- Cough and gag reflexes absent.
- Apnoea.

There should be no central nervous system depressant or muscle relaxant drugs present and metabolic, endocrine or hypothermic causes of coma should be excluded. Electroencephalography, cerebral angiography and evoked potentials are not included in the above criteria although they may assist in difficult cases (e.g. where physical signs are obscured, or altered by the presence of sedative or muscle relaxant drugs). Pallis in his series of articles entitled the 'ABC of Brain Stem Death' drew attention to pitfalls in the diagnosis of fixed dilated pupils and emphasized the importance of the history and context of the physical signs in avoiding diagnostic errors.[2]

A patient with Guillain-Barré syndrome managed in the intensive care unit of our hospital and who was totally paralysed, developed fixed dilated pupils during the course of his illness. This alerted us to the possibility of misdiagnosis of brain death if the criteria outlined above are used alone. Despite sensitive monitoring systems, ventilator mishaps may still occur, and cardiac arrhythmias associated with autonomic dysfunction are a recognised manifestation in Guillain-Barré syndrome.[3] These complications, although rare, can confuse the diagnosis of brain death, particularly if an anoxic insult occurs.

The purpose of this report is to alert the clinician to the possibility of misdiagnosis of brain death in the patient with severe Guillain-Barré syndrome who develops fixed dilated pupils, as well as to present a logical approach to the differential diagnosis of fixed dilated pupils.

CASE REPORT

A 36 year old farmer was admitted to the intensive care unit with a 48 hr history of progressive bilateral symmetrical sensorimotor peripheral neuropathy following an upper respiratory tract infection. On admission there was evidence of a flaccid tetraparesis with involvement of some cranial nerves. The pupils were fixed and dilated (although the extraocular muscle movements were normal) and there was bilateral VII nerve weakness. There was also weakness of the jaw muscles, partial weakness of muscles supplied by the XIth and XIIth cranial nerves, and cough and gag reflexes were markedly depressed.

By the seventh day his neurological state had worse-

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ned. While his pupils remained fixed and dilated, the extraocular muscle movements were now absent, along with an absent oculocephalic reflex, cough reflex and gag reflex. There was also no limb movement, and the peripheral reflexes could not be elicited. During this time there had been no catastrophic event, such as a ventilator disconnection or cardiac arrest, causing anoxia. Other causes of peripheral neuropathy such as hepatitis, porphyria, toxin ingestion, diphtheria and botulism were excluded. An EMG was performed which revealed a pattern consistent with the diagnosis of Guillain-Barre syndromé. The brain stem auditory evoked response testing was normal.

DISCUSSION

Although our patient satisfied some of the clinical criteria for brain death, this diagnosis was not considered for two reasons. Firstly, there was no evidence that the patient's condition was due to a disorder which could lead to brain death, and secondly the brain stem auditory evoked responses demonstrated intact brain stem function. Nevertheless, there often remains the potential for a ventilator mishap or cardiac arrest in these patients and, hence, the possibility of misdiagnosis of brain death by those not fully aware of the preconditions and diagnostic tests for confirmation of brain death.

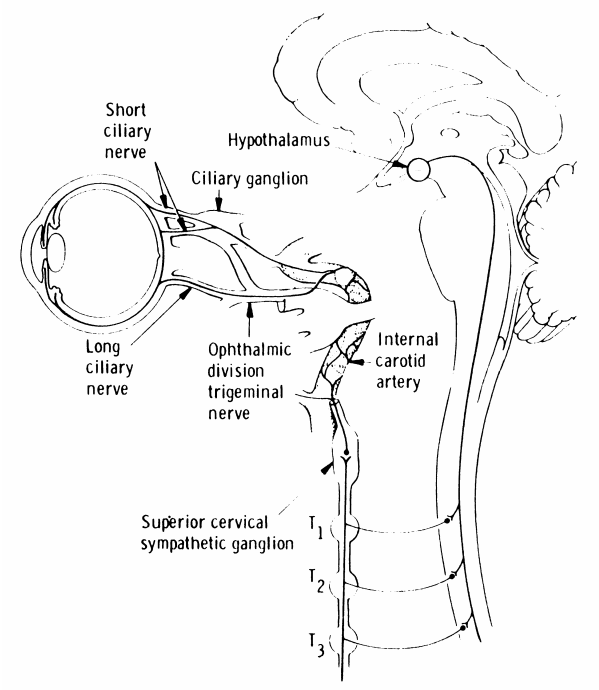

Figure 1. The sympathetic pupillodilator pathways (Modified from Plum F, Posner J. The diagnosis of Stupor and Coma. Contemporary Neurology Series. 3rd Ed. Philadelphia, Davis; 1980. p 41).

Sympathetic stimulation dilates the pupil and parasympathetic stimulation constricts it. Inhibition of either of these systems has the opposite effect. The resting pupil size represents a balance between the two systems, depending on light intensity or other factors such as local or systemic drug administration.

With regard to the parasympathetic pathways, approximately 10% of the afferent fibres that travel via the optic nerve and optic chiasm to the lateral geniculate bodies, relay in the periaqueductal grey matter to both Edinger-Westphal nuclei. Preganglionic efferent parasympathetic nerves are carried in the dorso-medial part of the oculomotor nerves and relay in the ciliary ganglion in the posterior orbit. The understanding of the microanatomy of these pathways is of great practical importance, as the external or peripherally placed pupillary fibres are vulnerable to direct pressure, and they are usually unaffected in infarction of the nerve trunk (which may occur in diabetes). The ciliary ganglion gives origin to 8 -10 short ciliary nerves that pass round the eye to reach to constrictor muscle of the pupil (figure 1).

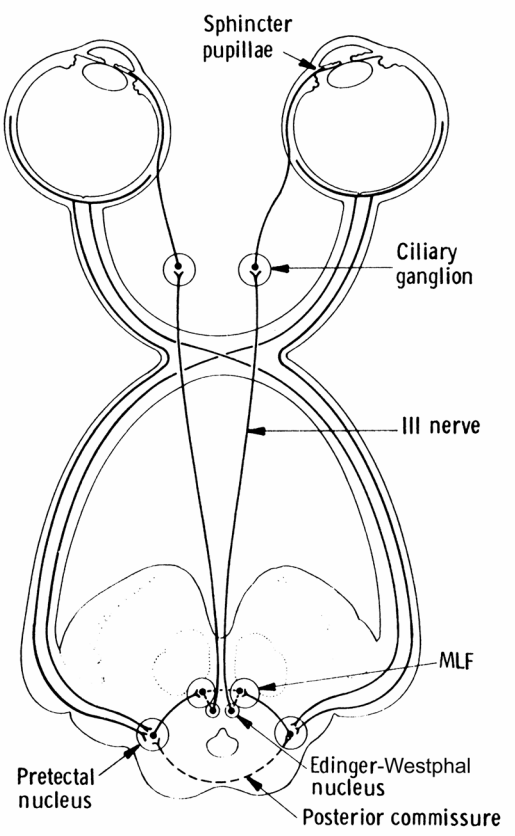

Figure 2. The parasympathetic pupilloconstrictor pathway. MLF = medial longitudinal fasiculus (Modified from Plum F, Posner J. The diagnosis of Stupor and Coma. Contemporary Neurology Series. 3rd Ed. Philadelphia, Davis; 1980. p 41).

The first neurone of the sympathetic innervation arises in the hypothalamus. The subsequent course is predominantly ipsilaterally through the brain stem, to the lateral gray matter of the thoracic spinal cord. It then travels via the superior cervical ganglion, carotid blood vessels, third cranial nerve, and nasociliary branch of the trigeminal nerve to reach the dilator muscle of the pupil as the long ciliary nerves (figure 2). From the level of the cavernous sinus outwards, the parasympathetic and sympathetic nerve fibres freely intermingle with each other, and in the third and fifth cranial nerves.

Having detected the presence of fixed dilated pupils, the diagnostic significance must be ascertained. If the patient is conscious, the significance of fixed dilated pupils is far less ominous, although the sign can provide a clue to an underlying disorder. Fixed dilated pupils, can be considered under the headings: Parasympathetic paralysis, sympathetic stimulation and a miscellaneous group, in which the mechanism of fixed dilated pupils is uncertain (Table 1).

Parasympathetic paralysis

Fixed dilated pupils can be caused by parasympatholytic or anticholinergic drugs. These drugs include atropine (mushroom poisoning),[4] scopolamine,[4] homatropine, cyclopentolate, quinine toxicity, tricyclic overdose, antihistamine overdose, glutethimide overdose,[4] trimetaphan and hypermagnesaemia.[5] Lesions affecting the third cranial nerve may, or may not, involve the pupillary fibres. Third nerve paralysis can be due to Guillain-Barré syndrome,[6,7,8] botulism (prevents acetyl-choline release), diphtheria toxin (damages the ciliary nerves), and raised intracranial pressure from any cause. Envenomation by some snakes (e.g. taipan, brown snake), funnel web spiders, and puffer fish can cause fixed dilated pupils by preventing acetylcholine release.[9-11]

Central nervous system involvement in syphilis, diabetes mellitus, brain stem encephalitis, pinealomas and multiple sclerosis can cause fixed dilated pupils, as can trauma due to brain injury or local damage of the ciliary nerves.

Sympathetic stimulation

Fixed dilated pupils can be associated with excessive endogenous catecholamine release from a phaeochromocytoma or from an overdose of sympathomimetic drugs including phenylephrine, ephedrine, cocaine, adrenaline, noradrenaline, dopamine[12] amphetamine or bretylium.[13]

Miscellaneous

Fixed dilated pupils can be associated with a miscellaneous group that includes cardiac arrest, cyanide poisoning, methanol poisoning,[14] propranolol overdose,[15] hypothermia, barbiturate overdose, benzalkonium chloride poisoning, excessively deep anaesthesia

FIXED DILATED PUPILS
(greater than 4 - 5mm)

PARASYMPATHETIC PARALYSIS		SYMPATHETIC STIMULATION		MISCELLANEOUS
DRUGS	**NEUROPATHY**	**DRUGS**	**PHAEOCHROMOCYTOMA**	
(Parasympatholytic)	**III Nerve Paralysis**	**(Sympathomimetic)**		
Atropine	Guillain Barre	Phenylephrine		Cardiac arrest
Scopolamine	Botulism	Ephedrine		Cyanide Poisoning
Homatropine	Diphtheria	Cocaine		Hypothermia
Cyclopentolate	Raised intracranial pressure	Adrenaline		Barbiturate overdose
Quinine toxicity	**CNS Diseases**	Noradrenaline		Methanol poisoning
Tricyclic overdose	Syphilis	Dopamine		Deep anaesthesia
Antihistamine overdose	Encephalitis	Amphetamine overdose		Propranolol overdose
Glutethimide overdose	Diabetes mellitus	Bretylium intoxication		Total spinal anaesthetic
Trimetaphan	Multiple sclerosis			Benzalkonium chloride
Hypermagnesaemia	Trauma			
	Envenomation			
	Snakes eg; Taipan			
	Funnel web spider			
	Puffer fish (tetrodotoxin)			
	Australian blue-ringed octopus			

Table 1. Classification of causes of fixed dilated pupils.

and a total spinal anaesthetic.[16]

Anoxia or ischaemia, if severe, may cause fixed dilated pupils. Experimentally, acute anoxia produces pupillary constriction until asystole occurs or the cardiac output is reduced by more than 70%, at which point the pupils dilate, only to return to mid position 3 to 20 minutes after death.

Fixed dilated pupils are an uncommon finding in the Guillain-Barré syndrome and may occur with or without extraocular muscle weakness. Coad *et al* reported a patient who presented in coma, with absent brainstem reflexes, in whom no diagnosis was initially obvious. A subsequent diagnosis of Guillain-Barré syndrome was made, and the patient made a full recovery.[8] There are no reported pathological studies available to explain this physical sign. The cause for fixed dilated pupils in this syndrome may be due to: a) demyelination of the post-ganglionic parasympathetic oculomotor fibres, which are among the few myelinated fibres of the post-ganglionic parasympathetic system, or b) autonomic dysfunction with excessive sympathetic overactivity. Anzai *et al*[6] and Williams *et al*[7] found that pharmacological testing of the pupils in patients who had Guillain-Barré syndrome and fixed dilated pupils suggested a postganglionic involvement of the parasympathetic and sympathetic nerves. Anzai *et al* believed that a demyelinating process of peripheral autonomic nerves was the most likely cause.

Over a 10 year period I have observed five patients with Guillain-Barré syndrome who developed fixed dilated pupils. In all cases both pupils were affected, suggesting that autonomic dysfunction may be the major contributor. All patients recovered.

In conclusion, while the clinical feature of 'fixed dilated pupils' is a valuable clinical sign it does not necessarily mean that the patient has severe brain injury. The importance of the history relating to the clinical setting is vital. A physiological approach to interpret this physical sign has been outlined.

Received 13 February 2000
Accepted 28 February 2000

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