Pupillary evaluation for differential diagnosis of coma

Y Tokuda, N Nakazato, G H Stein

OBJECTIVES: To determine the usefulness of bedside evaluation of pupils in determining the aetiology of coma by adopting a probabilistic approach.

PATIENTS AND METHODS: One hundred and fifteen consecutive patients presenting with coma were enrolled in this prospective cohort during the 12 month study period in the emergency room of a community teaching hospital. Patients underwent structured clinical examinations and laboratory and imaging tests. Assignment of aetiology of coma was based on strict adherence to predetermined criteria and achieved by consensus of the two physician investigators. One year follow up was obtained in all patients.

RESULTS: Aetiology of coma was determined in 98% of the patients. It was metabolic in 69 patients (60%) and structural in 46 patients (40%). Metabolic causes included drug overdose, acute alcohol intoxication, hypoglycaemia, sepsis, and pneumonia. Structural causes included intracerebral haemorrhage, subarachnoid haemorrhage, cerebral infarction, subdural haematoma, and epidural haematoma. Multivariate logistic regression analysis showed light reflex loss (likelihood ratio for positive test result 3.59) and anisocoria (likelihood ratio for positive test result 9.0) as independent predictors of structural origin.

CONCLUSIONS: In this prospective study of patients presenting to the emergency room of a community based teaching hospital with coma, in about 60% the coma is of metabolic origins and in about 40% of structural origins. Light reflex loss and anisocoria suggest a structural aetiology.

Coma can be defined as a state of unarousable unresponsiveness. The comatose patient cannot be aroused and a purposeful response cannot be provoked. Patients in a light coma respond to noxious stimuli with a variety of protective reflexes, whereas patients in a deep coma do not respond to pain. Mathematical scales based on neurological findings have also been developed to define altered mentation. The Glasgow coma scale (GCS) is the most widespread method, and a GCS score of 7 or less was used as a definition of coma.

Coma is one of the most common presentations in emergency department settings. It may be caused by a variety of disorders but these can be categorised into metabolic and structural origins. This differentiation is important as neurological interventions are sometimes needed in structural coma. Currently, individual clinical experience guides the physician for initial diagnosis of coma as there are only a few studies that describe the spectrum of aetiology. Since knowledge of disease probability is crucial in terms of differential diagnosis, relative frequency of various causes of coma should be investigated in an actual cohort.

Furthermore, probabilistic characteristics of simple bedside pupillary evaluation, such as light reflex and anisocoria, have not been well described, although major medical textbooks and review articles strongly recommend their use in initial evaluation of coma. The purpose of this study was to determine the disease probability of coma and the usefulness of light reflex and anisocoria in differentiating the aetiology.

METHODS

From January to December 1999, all patients 15 years of age and older presenting to the Okinawa Chubu Hospital emergency department with coma were registered. Patients presenting with out-of-hospital cardiopulmonary arrest were excluded.

The emergency physician history and physical examination were supplemented with a checklist. It was designed to record initial GCS score, size of each pupil, and status of light reflex. Anisocoria was defined as the difference of diameters of pupil more than 1 mm. Absence of light reflex was defined as no pupillary constriction to conventional bright penlight in at least one eye.

Standardised evaluation for all patients included detailed clinical history, complete physical examination with systematic neurological examination, and basic laboratory tests (measurement of blood glucose, serum electrolytes, blood urea nitrogen, and serum creatinine and electrocardiography and chest radiography). Cranial computed tomography, magnetic resonance imaging, cerebral angiography, or encephalography were performed when indicated clinically.

Both the checklist and the medical record were reviewed by one of the investigators. Patients who were admitted to the hospital were followed up as inpatients; all medical records were reviewed after one year. The protocol was evaluated and approved by the ethics committee of Okinawa Chubu Hospital.

Diagnostic criteria

All coma patients were categorised using the following criteria to define the cause of the coma. Firstly, the primary attending physician's discharge diagnosis was noted regarding the aetiology of coma. Secondly, this aetiology was intensively reviewed by one of the investigators to determine if it was the best probable explanation for the episode of coma based on all available information including laboratory tests, imaging tests, or necropsy findings. Lastly, when there was diagnostic disagreement, two of the investigators reached diagnostic consensus with the primary attending physician caring for the individual patient.

Structural origins of coma were defined as both supratentorial and subtentorial lesions with gross anatomical abnormality, including cerebrovascular disease, intracranial haematoma, tumour, and contusion. Metabolic origins of coma were primarily systemic disorders causing consciousness disturbances such as drug overdose, poisoning, hypoglycaemia,
electrolyte abnormality, cerebral hypoxia, infections not primarily in the central nervous system, or other metabolic process.

**Statistical analyses**

Standardised forms for entry of clinical, laboratory, and outcome data were utilised. Data management and analyses were conducted with the use of SPSS version 10 (SPSS Inc, Chicago, Illinois) software packages.

Statistical tests included the χ², Fisher’s exact, and Mann-Whitney non-parametric tests to evaluate differences between groups. Logistic regression analysis was used to test for independence of pupillary light reflex testing and presence of anisocoria in discrimination of structural versus metabolic aetiology of coma. Age, gender, and level of consciousness (score on the GCS at admission) were incorporated into logistic regression analysis as adjustments.

Test characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio for positive test for structural origin) were also calculated for pupillary light reflex and anisocoria.

**RESULTS**

Besides those who did not fit the emergency department admission criteria and were referred to the outpatient department, a total of 16 605 patients older than 14 years of age were treated in the emergency department during this period. One hundred fifteen patients met the entry criteria. Selected patients, a total of 16 605 patients older than 14 years of age were treated in the emergency department during this period. One hundred fifteen patients met the entry criteria.

The relative frequency of various causes of coma in our patients was similar to that observed in the classic textbook and the previous report despite geographic and technological differences. As 60% of coma is of metabolic origin, it is important to search for systemic causes in the initial evaluation, without immediate resort to cranial computed tomography.

Leading medical textbooks consistently support the idea that the presence or absence of light reflex is the single most important physical sign potentially distinguishing structural from metabolic coma; pupillary pathways are relatively resistant to metabolic insult. A unilateral, dilated, unreactive pupil may rarely be caused by an intrinsic ipsilateral midbrain lesion but most commonly is a result of compression of the third cranial nerve as occurs in transtentorial herniation.

However, these bedside tests have never been evaluated to determine probabilistic characteristics, such as sensitivity, specificity, and likelihood ratios. Since it is extremely
important to establish likelihood ratios of common clinical signs
in order to have a more solid scientific basis for clinical
diagnosis, even classic tests such as pupillary evaluations
should be evaluated in formal clinical research.4 As Luber et al
have highlighted, even simple hypoglycaemia may have a con-
fusing presentation of coma.15 Our results about likelihood
ratios of both light reflex loss and anisocoria now confirm
their importance as the strong clinical signs.

The limitations of this study should be acknowledged. First,
not all patients underwent all diagnostic tests. Cranial
computed tomography and magnetic resonance imaging were
performed less frequently in patients for whom the aetiology
was assigned as of metabolic origin. We believe that this is not
a major limitation because most metabolic diseases were con-
ﬁrmed in the long patient follow up period. Furthermore, no
structural aetiologies were missed in those patients with both
an initial diagnosis of a metabolic cause and no imaging stud-
ies. Second, we excluded patients with out-of-hospital cardio-
pulmonary arrest because they were dead on arrival with no
resuscitation or studies attempted. Lastly, we used a GCS score
of more than 7 points to exclude subjects from our study
because we focused on comatose patients, although Vilke et al
point out the importance of clinical judgment to include
significant structural damage in non-coma patients with a
normal neurological examination.16 The probability of a metabolic aetiology is nearly 60% and a
structural aetiology 40% for comatose patients presenting to
an emergency department. For the first time, our analysis
shows simple pupillary evaluation as an important bedside
examination in differential diagnosis of coma.

ACKNOWLEDGEMENTS
These data were presented at a poster session at the annual meeting of
the Japanese Society of Internal Medicine, March, 2001. The study
was funded by St Luke’s Life Science Institute, Tokyo, Japan.

Authors’ affiliations
Y Tokuda, N Nakazato, G H Stein, Division of General Internal
Medicine, Department of Medicine, Okinawa Chubu Hospital, Okinawa,
Japan

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Independent predictors for structural causes of coma; results are % (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Absence of the light reflex</td>
<td>83 (76 to 90)</td>
</tr>
<tr>
<td>Anisocoria</td>
<td>39 (30 to 48)</td>
</tr>
</tbody>
</table>

REFERENCES
1 Fisher CM. The neurological examination of the comatose patient. Acta
2 Rosen P. Emergency medicine: concepts and clinical practice. 4th Ed.
3 Plum F, Posner J. The diagnosis of stupor and coma. 3rd Ed.
literature: XV. How to use an article about disease probability for
differential diagnosis. Evidence-Based Medicine Working Group. JAMA
1999;281:1214–9.
5 Anonymous. A new arrival: evidence about differential diagnosis
(editorial). ACP Journal Club 2000;133(3).
6 Malik K, Hess DC. Evaluating the comatose patient. Rapid neurologic
assessment is key to appropriate management. Postgrad Med
2002;111:38–40, 43–6, 49–50 (passim).
7 Simon R. Coma and disorders of arousal. In: Cecil R, Bennett J,
9 Chang GY. Emergency evaluation of the comatose patient. Hosp Pract
10 Wilhelm H. Neurro-ophthalmology of pupillary function—practical
16 Spencer JA. Czarniecki JS. The pupil in stroke. Can J Ophthalmo1
17 Boettner UW. Ocular motor dysfunction in stupor and coma. Baillieres
18 Chesnutt RM, Gautelle T, Blunt BA, et al. The localizing value of
asymmetry in pupillary size in severe head injury: relation to lesion type
as head trauma: a report of four cases. Am J Emerg Med
20 Vilke G, Chan T, Guss D. Use of a complete neurological examination
to screen for significant intracranial abnormalities in minor head injury. Am
Pupillary evaluation for differential diagnosis of coma

Y Tokuda, N Nakazato and G H Stein

Postgrad Med J 2003 79: 49-51
doi: 10.1136/pmj.79.927.49

Updated information and services can be found at:
http://pmj.bmj.com/content/79/927/49

These include:
References
This article cites 14 articles, 0 of which you can access for free at:
http://pmj.bmj.com/content/79/927/49#BibL
Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Emergency medicine (129)
- Ophthalmology (101)
- Diabetes (142)
- Drugs misuse (including addiction) (35)
- Epidemiology (401)
- Metabolic disorders (221)
- Occupational and environmental medicine (37)
- Pneumonia (respiratory medicine) (28)
- Stroke (137)
- Unwanted effects / adverse reactions (37)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/