Pupillary evaluation for differential diagnosis of coma

Y Tokuda, N Nakazato, G H Stein

Objective: 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 haematomata. 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 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 electroencephalography 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 features of the enrolled patients are shown in table 1. Age, gender, and level of consciousness (median score on the GCS) were not significantly different between patients with metabolic causes and patients with structural causes (table 1).

A final aetiology for coma was assigned in 113 (98%) patients. The specific aetiologies are listed in table 2. Overall, 60% of the patients had coma of a metabolic origin and 40% a structural origin. Two patients had coma of unknown aetiology; it was classified as of metabolic origin based on the final decision of the primary physician and the investigators.

A multivariate logistic regression model adjusting for age, gender, and level of consciousness showed that light reflex loss (odds ratio 11.02, 95% confidence interval 3.9 to 30.9; p=0.001) and anisocoria (odds ratio 7.5, 95% confidence interval 1.4 to 39.4; p=0.021) were independent predictors of coma of metabolic origin (odds ratio 11.02, 95% confidence interval 3.9 to 30.9; p=0.001) and anisocoria (odds ratio 7.5, 95% confidence interval 3.9 to 30.9; p=0.001) and anisocoria (odds ratio 7.5, 95% confidence interval 3.9 to 30.9; p=0.001). Since it is extremely important physical sign potentially distinguishing structural versus metabolic aetiology of coma, we present these issues. A standardised manner. It extends the previous conclusions on aetiology of coma and provides information on recent clinical situations using modern imaging technology.

The frequency of various causes of coma in our patients was similar to that observed in the classic textbook [1] and the previous report [2] 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. [3] Normal size, shape, and response to light indicate intact midbrain function and usually exclude midbrain damage as the cause of coma. [4] 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. [5]

However, these bedside tests have never been evaluated to determine probabilistic characteristics, such as sensitivity, specificity, and likelihood ratios. Since it is extremely

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**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th>Total</th>
<th>Structural</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>115</td>
<td>46 (40)</td>
</tr>
<tr>
<td>Median age</td>
<td>52</td>
<td>57.5</td>
</tr>
<tr>
<td>Range</td>
<td>15-99</td>
<td>15-91</td>
</tr>
<tr>
<td>Female (%)</td>
<td>52</td>
<td>24 (52.2)</td>
</tr>
<tr>
<td>Median Glasgow coma scale</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Eye</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Motor</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Verbal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Absence of the light reflex (%)</td>
<td>54 (47)</td>
<td>38 (82.6)</td>
</tr>
<tr>
<td>Anisocoria (%)</td>
<td>21 (18.3)</td>
<td>18 (39.1)</td>
</tr>
</tbody>
</table>

**Table 2** Causes of coma

<table>
<thead>
<tr>
<th>No</th>
<th>(%) (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Structural</td>
<td></td>
</tr>
<tr>
<td>Brain haemorrhage</td>
<td>20</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>9</td>
</tr>
<tr>
<td>Brain infarction</td>
<td>5</td>
</tr>
<tr>
<td>Subdural haematoma</td>
<td>4</td>
</tr>
<tr>
<td>Epidural haematoma</td>
<td>3</td>
</tr>
<tr>
<td>Brain contusion</td>
<td>2</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>1</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Central pontine myelinolysis</td>
<td>1</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This study aimed to address the prevalence of the aetiologies of coma and to elucidate probabilistic characteristics of pupillary evaluation, as few studies have reported these issues. A description of causes of stupor or coma in a classic textbook published in 1980 reported on the disease probability of 500 patients, but information on inclusion criteria and study setting was not provided. [3]

The current study was based on an emergency department cohort of patients with coma who had been evaluated in a standardised manner. It extends the previous conclusions on aetiology of coma and provides information on recent clinical situations using modern imaging technology.

The frequency of various causes of coma in our patients was similar to that observed in the classic textbook [1] and the previous report [2] 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.

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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. As Luber et al have highlighted, even simple hypoglycaemia may have a confusing presentation of coma.19 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 confirmed 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 studies. 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.20

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 supports simple pupillary evaluation as an important bedside examination in differential diagnosis of coma.

ACKNOWLEDGEMENTS

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REFERENCES


Table 3: Independent predictors for structural causes of coma; results are % (95% confidence interval)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Likelihood ratio</th>
</tr>
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<tbody>
<tr>
<td>Absence of the light reflex</td>
<td>83 (76 to 90)</td>
<td>77 (69 to 85)</td>
<td>70 (62 to 79)</td>
<td>87 (81 to 93)</td>
<td>3.56</td>
</tr>
<tr>
<td>Anisocoria</td>
<td>39 (30 to 48)</td>
<td>96 (92 to 99)</td>
<td>86 (79 to 92)</td>
<td>70 (62 to 79)</td>
<td>9</td>
</tr>
</tbody>
</table>