Validation of a clinical classification for subtypes of acute cerebral infarction

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Abstract
The validity of a clinical classification system was assessed for subtypes of cerebral infarction for use in clinical trials of putative stroke therapies and clinical decision making in a population based stroke register (n = 536) compiled in Perth, Western Australia in 1989-90. The Perth Community Stroke Project (PCSS) used definitions and methodology similar to the Oxfordshire Community Stroke Project (OCSP) where the classification system was developed. In the PCSS, 421 cases of cerebral infarction and primary intracerebral haemorrhage (PICH), confirmed by brain imaging or necropsy, were classified into the subtypes total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS), and posterior circulation syndrome (POCS). In this relatively unselected population, relying exclusively on LACS for a diagnosis of PICH had a very low sensitivity (6%) and positive predictive value (3%). Comparison of the frequencies and outcomes (at one year after the onset of symptoms) for each subgroup of first ever cerebral infarction in the PCSS (n = 248) with the OCSP (n = 543) registers showed uniformity only for LACI. For example, there were 27% of cases of TACI in the PCSS compared with 17% in the OCSP (difference = 10%; 95% confidence interval 95% CI 4% to 16%) and 15% of cases in the PCSS compared with 24% in the OCSP were POCI (difference = 9%; 95% CI 3% to 15%). Case fatalities and long term handicap across the subgroups were not significantly different between studies, but the frequencies of recurrent stroke were significantly greater for POCI in the OCSP compared with the PCSS. Although this classification system defines subtypes of stroke with different outcomes, simple clinical measures—level of consciousness, paresis, disability, and incontinence at onset—are more powerful predictors of death or dependency at one year. It is concluded that simple clinical measures that reflect the severity of the neurological deficit should complement this classification system in clinical trials and practice.

Although substantial progress has been made in developing strategies for the prevention of stroke, there is still no effective treatment for the acute event; but a number of putative treatments for stroke are now undergoing evaluation in multicentre clinical trials. A crucial issue associated with such trials is the classification of cerebral infarction because it may arise from several different pathophysiological processes with variable prognosis. Ignoring major prognostic factors in the analysis of clinical trials increases the background variability of patients and may obscure differences in the efficacy of treatments.

Despite the recognition that pathological homogeneous stroke entities need to be identified and studied, however, the usefulness of various criteria and scoring systems for epidemiological research, particularly clinical trials, is limited. Although CT differentiates accurately haemorrhage from infarction, there are differences in the quality and interpretation of CT across centres, and access of patients to this investigation is not available or often delayed in many countries. Moreover, it is often impractical to perform other objective investigations such as angiography, particularly if the benefit of treatment is dependent on minimising the delay between the onset of symptoms and the start of treatment.

The realities of the numbers of patients required to produce meaningful results from clinical trials dictate that a classification of stroke should be valid and reliable, yet simple enough to facilitate the recruitment of patients and to allow the conclusions of the trial to be communicated easily and applied widely. Bamford et al. considered these issues in a study that introduced a classification system for cerebral infarction based on their experience in the Oxfordshire Community Stroke Project (OCSP), a population based study of first ever stroke. They defined by simple clinical variables four subtypes of cerebral infarction that had different patterns of case fatality, recurrence, and long term disability. This classification is not only useful in clinical practice, but could increase the sensitivity of clinical trials by correcting for imbalances in study groups or improving the precision of the estimates of differences between treatments. The purpose of our study was to validate this classification system in patients registered in the Perth Community Stroke Study (PCSS), a population based study of acute cerebrovascular disease in
Perth, Western Australia. The PCSS used standard definitions, measurements of outcome, and community-wide methods of case ascertainment that were similar to those used in the OCSP.

Methods
THE PERTH COMMUNITY STROKE STUDY (PCSS) POPULATION
The objectives, design, and study population of the PCSS have been described. In brief, the aims of the study were to determine the incidence, aetiology, and outcome of acute stroke (n = 536) in a geographically defined and representative segment (population 138 708) of Perth, Western Australia, during an 18 month period in 1989–90. The register used a variety of overlapping sources that included notifications from general practitioners; scrutiny of attendances at, and admissions to, all acute hospitals, rehabilitation centres, and nursing homes in and around the study area; coroner’s reports and death certificates; and surveillance of computerised hospital discharge statistics that cover all inpatient separations from every hospital in the state.

EVALUATION OF PATIENTS
Most patients (83%) were seen early after onset of the event (median delay five days) by a single observer (CSA) who conducted a standardised interview and physical examination. Those patients who were not personally assessed were classified as cases on the basis of the history and neurological examination obtained from the medical records. Standard World Health Organisation (WHO) criteria were used for stroke and each event was classified as being either the patient’s first ever in a lifetime (first ever) or recurrent event during the study period. Criteria were applied that combined clinical data with the results of CT, MRI, or necropsy so that strokes could be classified into several “pathologically distinct” groups (in 86% of cases).

Information obtained from each patient at baseline included data on associated illnesses, risk factors for cardiovascular diseases, and the patterns of disability within the immediate premorbid period. If the patient was unconscious or otherwise not assessable, information was obtained from the patient’s closest relative or another reliable proxy, or hospital records, or the general practitioner. Level of consciousness at onset was measured by the Glasgow coma scale, and scores 3–9 and 10–14 were classified as “comatose” and “drowsy” respectively. Degree of paresis was measured with the motricity index, which gives a score from 0 (total plegia) to 100 (normal). We defined a score of 0–50 as “severe paresis”, 51–94 as “moderate paresis”, and a score of 95–100 as “normal or minimal paresis”. Comorbid diseases of interest were diagnosed on the basis of available information and were considered to be present if they occurred at any time before the onset of the index event. Hypertension was defined if a patient had a clinical history of hypertension, or had two or more previously documented systolic blood pressures $\geq 160$ mm Hg or diastolic blood pressures $\geq 95$ mm Hg. Coronary heart disease was defined as a history of acute myocardial infarction or angina pectoris. Peripheral vascular disease (PVD) was diagnosed if the patients had a history of intermittent claudication (WHO criteria: calf pain induced by exercise and relieved within 10 minutes by rest, that was atherosclerotic in origin). Diabetes mellitus was deemed present if the patient gave a history of the condition that was confirmed in the medical records, or there was a random blood glucose concentration of $\geq 11$ mmol/l.

The same investigator who made the baseline assessments prospectively followed patients until 12 months after their index event or the time of death if it occurred before that date. All survivors were reassessed at four and 12 months, generally in their own home or at the place of residence, and were classified as “independent” (score 0–3) or “dependent” (4–5) according to the Oxford handicap scale. Any patient who gave a history of a recurrent stroke during follow up was reassessed with the same baseline assessment schedule. Human rights and ethics committee approved the study at each participating institution.

CLASSIFICATION OF SUBTYPES OF STROKE
For this report, one of us (BVT) reviewed details of the neurological examination for each event that was recorded on the original assessment forms while blind to the final pathological diagnoses and outcomes. Each stroke event was then classified into one of the four clinical syndromes outlined in detail by Bamford et al. The appendix includes an outline of these specific subgroups—namely, total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS), and posterior circulation syndrome (POCS). When brain imaging or necropsy had excluded primary intracerebral haemorrhage (PICH), the subgroups were referred to as infarcts: total anterior circulation infarcts (TAI), partial anterior circulation infarcts (PACI), lacunar infarcts (LACI), and posterior circulation infarcts (POCI).

BRAIN IMAGING AND NECROPSY
Considerable effort was made to ensure that information about the nature and extent of cerebral lesions could be correlated with the various clinical syndromes and outcomes. All CT and MRI films and necropsies were reviewed by a study neuroradiologist or neuropathologist blind to clinical and other information, and each cerebral region that contained infarction or haemorrhage was quantified. By contrast with Bamford et al., we did not use the Guy’s Hospital stroke diagnostic scale to exclude PICH in those cases where brain imaging was unavailable, and cases of “undetermined stroke” were not reclassified into one of the mentioned clinical syndromes. In the PCSS, infarcts associated
with first-ever strokes were coded into one of the following sites: deep (caudate, putamen, globus pallidus, thalamus, internal capsule, and deep periventricular white matter); lobar (specific cortical and subcortical locations); and brainstem (including cerebellum). The deep lesions were further subdivided according to size, which was estimated by multiplying the greatest sagittal, transverse, and coronal measures from the brain imaging or brain slices. These lesions were then categorized as either “small” (<8 cm³) or “large” (≥8 cm³) to differentiate lacunar infarcts from larger striatocapsular infarcts, which may have different aetiologies. If no relevant acute cerebral lesion was documented, the site of infarction was classified as “unknown”.

STATISTICAL ANALYSIS

The sensitivity, specificity, and positive predictive value of LACS for PICH was calculated from a standard 2 x 2 contingency table on the study population minus cases of subarachnoid haemorrhage (SAH) and undetermined stroke; clinical subgroups (“test”) were then compared with pathology (the “standard”). The validity of the clinical subgroups with respect to the site of first-ever cerebral infarction as measured by brain imaging or necropsy was ascertained by the χ² test for categorical variables. All p values were two-tailed; values < 0.05 were considered to indicate statistical significance. Comparability of the PCSS (Perth) and OCS (Oxford) study groups with respect to baseline characteristics and outcomes for first-ever cerebral infarction was ascertained. Estimates of difference and 95% confidence intervals (95% CIs) for differences were calculated by subtracting the Perth value from the Oxford value, and reported according to methods outlined by Gardner and Altman. Kaplan-Meier statistics for various baseline variables for first-ever cerebral infarcts in the PCSS were estimated from onset to one year after stroke. Follow-up was censored at the time of death or dependency at one year. Independent predictors of death or dependency at one year were identified from a Cox proportional hazards model that was constructed by forwards stepwise regression. All the data were analysed on SPSS PC for Windows software, except the Cox regression models, which were constructed with EGRET software.

Results

ALL STROKES: PCSS

Over the 18 month study period of the PCSS, 492 patients experienced a total of 536 strokes: 261 men (52%) and 255 (48%) women (mean age (SD) 73 (13), range 13–96 years). Cerebral infarction accounted for 382 (71%; 95% CI 66–76%) events, PICH 60 (11%; 95% CI 11–17%), and SAH 19 (4%; 95% CI 2–6%). In 75 events (14%; 95% CI 17–23%) the cause of the stroke was undetermined. Twenty per cent of all cases were managed outside hospital during the acute phase of the illness and no patient was lost to follow up. Among the 492 patients in this study, 235 (48%) were either dead or had impaired communication due to aphasia or altered consciousness at the time of baseline assessment. In these cases, data concerning the onset of the stroke and other medical and social factors were obtained from a close relative or friend, and in only 20 (4%) patients were medical records or death certificates used as the sole source of information on the study variables.

Data on the severity of paresis, level of consciousness, and the presence or absence of incontinence were not available in 34%, 10%, and 11% of cases respectively. The distributions of age, sex, and risk factors for these events were similar to those with complete data. Patients with missing data were significantly more likely, however, to have died within the first four days after onset, to have been inactive, and to have lived in a nursing home, compared with other cases (all p < 0.05).

Thus of the 442 strokes (first ever and recurrent) due to cerebral infarction and PICH confirmed by brain imaging or necropsy, 421 (95%) cases had sufficient clinical details recorded on the original PCSS assessment forms to allow classification into one of the four defined clinical syndromes. These were classified as TACS (30%), PACS (29%), LACS (24%), or OCPS (12%). The proportional frequencies of PICH among these subgroups were 21% (28/134), 13% (17/126), 3% (3/106), and 11% (6/55). Table 1 shows the calculation of indices for the LACS as a diagnostic test for PICH in this population. The data show that PICH has a very low likelihood of presentation as LACS.

Table 1

<table>
<thead>
<tr>
<th>LACI</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>a</td>
<td>b</td>
<td>106</td>
</tr>
<tr>
<td>Negative</td>
<td>c</td>
<td>d</td>
<td>315</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>367</td>
<td>421</td>
</tr>
</tbody>
</table>

Incidence of PICH = 100 x (a + b)/ (a + b + c + d) = 13%
Sensitivity = 100 x a/(a + c) = 67%
Specificity = 100 x d/(b + d) = 72%
Positive predictive value = 100 x a/(a + b) = 53%
Negative predictive value = 100 x d/(c + d) = 84%
Likelihood ratio = sensitivity/(1–specificity) = 0.21

FIRST EVER CEREBRAL INFARCTS: COMPARISON OF THE PCSS AND OCS

To make meaningful comparisons between the PCSS and OCS studies, further analysis of the data was restricted to first-ever cerebral infarcts. Of the 259 cases of first-ever cerebral infarction in the PCSS, 248 (96%) were reclassified into the clinical subtypes by CT in 219 (88%), MRI in 14 (6%), and necropsy in 15 (6%). Table 2 compares the characteristics of the first-ever cerebral infarcts in the Perth
Table 2 Demographic characteristics of first-ever cerebral infarction in the study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Perth</th>
<th>Oxford</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>248</td>
<td>543</td>
<td></td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>73</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Men (%)</td>
<td>54</td>
<td>50</td>
<td>4 (-3 to 11)</td>
</tr>
<tr>
<td>Time to assessment (median days)</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pathological confirmation (%)</td>
<td>100</td>
<td>81</td>
<td>19 (6 to 32)</td>
</tr>
<tr>
<td>Independent prestroke (%)</td>
<td>79</td>
<td>85</td>
<td>-6 (-12 to 0)</td>
</tr>
</tbody>
</table>

Table 3 Comparison of proportional frequencies (% of clinical subgroups of first-ever cerebral infarction in Perth and Oxford

<table>
<thead>
<tr>
<th>Group</th>
<th>Perth (n = 248)</th>
<th>Oxford (n = 543)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACI</td>
<td>27</td>
<td>17</td>
<td>10 (4 to 16)</td>
</tr>
<tr>
<td>PACI</td>
<td>30</td>
<td>34</td>
<td>4 (-3 to 11)</td>
</tr>
<tr>
<td>LACI</td>
<td>28</td>
<td>25</td>
<td>3 (-4 to 10)</td>
</tr>
<tr>
<td>POCI</td>
<td>15</td>
<td>24</td>
<td>-9 (-3 to -15)</td>
</tr>
</tbody>
</table>

TACI = Total anterior circulation infarcts; PACI = partial anterior circulation infarcts; LACI = lacunar infarcts; POCI = posterior circulation infarcts

and Oxford populations. Before the index stroke, the patients in Perth were more likely to be dependent than the patients in Oxford, but the age and sex distributions and time to assessment were similar. As highlighted previously, the PCSS included cases of cerebral infarction defined by CT, MRI, or necropsy, whereas 19% of cases in the OSCP had a low probability of PICH on the basis of their score on the Guy's Hospital stroke diagnosis scale.

Table 3 shows the proportional frequencies of the clinical subtypes of first ever cerebral infarction in the two populations. The proportion of PACI and LACI were similar, but Perth had a significantly greater proportion of TACI and correspondingly fewer POCI compared with Oxford. It was important, therefore, to determine whether these differences were real and not related to misclassification. Table 4 shows that the overall and subgroup specific case fatalities and long term dependencies did not differ significantly between the centres (although the 95% CIs were wide). The prognosis in terms of recurrent stroke for TACI and LACI was also similar in the centres. A significantly higher proportion of patients with PACI and POCI, however, had recurrent events in Oxford, yet these patients seemed to be less likely to remain dependent at one year after stroke compared with Perth.

PREDICTION OF LESION LOCATION

Table 5 shows a statistically significant trend across subgroups (p < 0.0001) indicating that these syndromes predict accurately the site of cerebral infarction. This trend would be even more significant if among the POCI subgroup, the case with a deep cerebral lesion (based within the internal capsule) and three out of the seven lobar lesions (which were located within an occipital lobe) were reclassified into brainstem category because of the common major vascular supply to these territories.

PREDICTORS OF DISABILITY FREE SURVIVAL

The baseline factors found on univariate analysis to be associated with death or dependency at one year in the PCSS were: age, clinical syndromes; marital state; premorbid dependency; level of consciousness; incontinence; severity of paresis; and disability (table 6). In the stepwise Cox proportional hazards model, one year mortality or dependency was associated in the derivation set with being comatose at onset, urinary incontinence, severe paresis, and both moderate and severe disability at onset; and evidence of peripheral vascular disease (table 7). The clinical subtypes did not enter the model as independent predictors of outcome.

Discussion

We wished to assess the validity of a classification system for infarction based on defined clinical syndromes that seems useful for clinical decision making and clinical trials. Our data highlight two important issues relevant to the development, evaluation, and application of
The classification system derived from the OCSP for cerebral infarction by Bamford et al.\(^4\) demonstrates good content and construct validity. It was developed by an eminent team with extensive clinical and research experience in cerebrovascular disease. Our study shows that this classification system also has good criterion validity. The clinical syndromes correspond accurately with lesions in different vascular territories as defined by CT, MRI, or necropsy as the reference. Nevertheless, we recognise the limitations of CT in defining the site of ischaemic lesions early after the onset of stroke, exemplified by between 15% and 44% of cases in each of the subgroups without a lesion visible on brain imaging.

It is important to note that the proportional frequencies and outcomes for the subgroups in the PCSS and OCSP showed inconsistent and significant patterns of differences. To begin with, a greater proportion of patients with TACI and a smaller proportion of patients with POCI were identified in the Perth compared with the Oxford group, whereas the proportional frequencies of PACI and LACI were similar in the two groups. This may have been due to misclassification, particularly as the present study used a retrospective analysis of data that was based on the signs at presentation rather than the classification being recorded prospectively on the maximal neurological deficit as defined by the OCSP. In the PCSS, not all patients were examined by a neurologist in the acute stage, and the presence of localising brainstem or posterior fossa signs may have been missed. It is apparent that the elucidation and interpretation of neurological signs depends on the experience of clinicians, the timing of the examination, and the conscious state of the patient.\(^14\) Whereas there is good agreement among examiners for paresis, there may be less than 50% agreement in the evaluation of sensory, visual, and brainstem signs.\(^14\) Furthermore, distant lesions within the vertebrobasilar vascular territory can produce signs such as hemianopia and aphasia identical to those of anterior circulation infarcts.\(^15\) Therefore, extrapolating information from the medical records of patients who died early after onset may have resulted in some POCI having been missed or misclassified as TACI. Conversely, the OCSP may have included cases that were not stroke, particularly as only two-thirds of the cases had brain imaging performed early after onset.

Misclassification between TACI and POCI is not, however, supported by the data on outcome. The case fatalities for each of the subgroups were consistent, although the confidence intervals were wide. If more POCI were classified as TACI in the PCSS, we would have expected differences in the frequencies of recurrent stroke and long term dependency for the subgroups. In fact, these outcomes were remarkably similar in the two studies. LACI was the only subgroup to show uniform figures for proportional frequency, case
Although haemorrhage, because of stroke is relatively good, have shown treatment was required. The necessity for stroke syndrome, respectively. In clinical decisions are made with great confidence and the risk of mistaking a non-vascular lesion for stroke is small. Accurate differentiation of haemorrhage from infarction (except for SAH), however, in the acute period requires CT. Given delays in the access of patients to CT and the necessity of early treatment to alter favourably the sequence of events after cerebral infarction, entry into a trial of treatment could proceed safely if the probability of haemorrhage was very low and the risk of treatment was low, and that diagnostic confirmation could be performed at a later date. Although an infrequent stroke syndrome with a relatively good prognosis in terms of mortality and long term disability, our findings suggest that patients with LACS could probably enter a clinical trial before brain imaging because of the low probability of underlying haemorrhage.

Although the OCSP classification system defines subgroups of stroke with different outcomes, it seems that the risk of death or dependency is best gauged from clinical variables, such as the level of consciousness, severity of paresis, and disability, and the presence of urinary incontinence at onset, that reflect the severity of the neurological deficit rather than the presumed pathophysiological mechanisms. In this study, patients who were comatose, incontinent, or severely plegic at presentation had some two to three times the risk of death or handicap by one year after first ever cerebral infarction compared with alert, continent, or non-paretic patients respectively. As loss of consciousness is by definition inconsistent with the diagnosis of lacunar infarction, the effect of these factors is consistent with clinical findings.

Many other predictors of death during the acute phase have been identified including various neurological signs such as papillary reaction, gaze paresis, and extensor plantar responses, various measures of disability, and some biochemical markers such as blood glucose concentrations. Some of these items form the basis of assessment scales such as the Canadian neurological scale and the National Institutes of Health (NIH) scale. Although various predictive equations using several variables generate values that correlate with outcome, no model yet examined has been shown to be sufficiently accurate—that is, to account for sufficient a proportion of the variation in outcome—to be used as a basis for clinical decisions about individual patients with stroke. In the light of these difficulties, the importance of simple measures as opposed to complex models has been emphasised.

The implication from this study is that: (a) the OCSP clinical classification is a valid measure of the underlying vascular territory for cerebral infarction; (b) it may allow patients presenting with LACS to be randomised into trials before diagnostic confirmation of infarction because the likelihood of underlying haemorrhage is extremely low; (c) simple measures that reflect the severity of the neurological damage, however (loss of consciousness, incontinence, paresis, and extent of disability) used in conjunction with the clinical classification allow the best discrimination between groups with different prognoses.

We are indebted to the National Health and Medical Research Council, the Australian Brain Foundation, and the Royal Perth Hospital Medical Research Foundation who supported the study; to Professor B Kakulas and Associate Professor T Chakera for reviewing the necropsy data and brain imaging scans respectively; and to the patients, their families, and the local medical staff who participated in this study. This work was supported by grants from the National Health and Medical Research Council, the Australian Brain Foundation, and the Medical Research Foundation of Royal Perth Hospital.

Appendix

DEFINITIONS FOR SUBTYPES OF CEREBRAL INFARCTION

Total anterior circulation infarcts (TACI)

These were defined as acute stroke with the combination of new higher cerebral dysfunction (for example, dysphasia, dyscalculia, visuospatial disorder); homonymous visual field deficit; and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm, and leg. If the conscious level was impaired and formal testing of higher cerebral function or visual fields was not possible, a deficit was assumed to be present.

Partial anterior circulation infarcts (PACI)

These were defined as only two of the three components of the TACI, with higher cerebral dysfunction alone, or with a motor/sensory deficit more restricted than those classified as LACI (for example, confined to the limb, or to face and hand, but not to the whole arm).

Lacunar infarcts (LACI)

These were defined as an acute onset of one of the five major recognised lacunar syndromes: pure motor stroke, pure sensory stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome, or sensory-motor stroke.

Posterior circulation infarcts (POCI)

These were defined as acute onset of focal neurological deficit that included any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; disorder of conjugate eye movement; cerebellar dysfunction without ipsilateral long-tract deficit (for example, ataxic hemiparesis); or isolated homonymous visual field deficit.

The pupil

Sir Thomas Browne's observations on the pupillary responses to light and shade befit his stature as a Fellow of the Royal College of Physicians. Both Victor Hugo and Thomas Hardy confuse the dark adaptation of the retina with the more rapid pupillary reaction to dark. It has been estimated that dark adaptation takes up to half an hour after a sudden transition from light to relative darkness. Thomas Mann's observations on Felix Krull are intriguing. The capacity for some people to dilate their pupils voluntarily is well recognised, but I have had difficulty finding any authority who believes in voluntary meiosis, other than that occurring as a result of convergence spasm. Duke-Elder gives one reference, in the German literature, to hysterical meiosis. Dickens' observations here, as almost always, are apposite. Whatever he found, Eugene Wrayburn's surgeon gave a gloomy prognosis, confirming, not for the first time, the fallibility of the medical profession in predicting the outcome of head injury.

Sir Thomas Browne, 1658, The garden of Cyrus
And therefore in diffused and open aspects, men holow their hand above their eye, and make an artificial brow, whereby they direct the dispersed rays of sight, and by this shade preserve a moderate light in the chamber of the eye; keeping the pupilla plump and fair, and not contracted or shrunk as in light and vagrant vision.

Victor Hugo, 1862, Les misérables
The pupil dilates in darkness and in the end finds light, just as the soul dilates in misfortune and in the end finds God.

Charles Dickens, 1864-5, Our mutual friend
He appeared irresistible. He did not retain it, but laid it gently down, took a candle, looked more closely at the injuries on the head, and at the pupils of the eyes. That done, he replaced the candle and took the hand again.

Thomas Hardy, 1887, The woodlanders
For her eyes were fresh from the blaze, and here there was no street lamp or lantern to form a kindly transition between the inner glare and the outer dark... but the pupils of her young eyes soon expanded, and she could see well enough for her purpose.

Thomas Mann, 1954, Confessions of Felix Krull, confidence man
It is a well-known fact that the muscles controlling the pupils of our eyes react involuntarily to the intensity of the light falling upon them. I decided to bring this reaction under voluntary control. I would stand in front of my mirror, concentrating all my powers in a command to my pupils to contract or expand... but later I actually succeeded in contracting them to the merest points and then expanding them to great, round mirror-like pools.

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NEUROLOGY IN LITERATURE


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