Probability Theory in the Diagnosis of Cushing's Syndrome

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ABSTRACT. In the differential diagnosis of patients in whom Cushing's syndrome is suspected, the physician uses clinical signs and simple laboratory data in addition to information gained from past experiences to make a decision concerning the probability of the diagnosis and the need for further investigation. He usually does not make an explicit formulation of either the information or the reasoning process leading to his decision. This report is an examination of an explicit method for estimating the probability of Cushing's syndrome in patients in whom this diagnosis is suspected, using clinical signs and simple laboratory techniques, not including steroid analyses. The clinical and nonsteroid laboratory data of 211 patients investigated for Cushing's syndrome were examined to determine the incidence of the signs of the syndrome in the patients with and without the disorder. These data were used to calculate the probability of Cushing's syndrome in 111 additional patients examined because Cushing's syndrome was suspected. The diagnosis of Cushing's syndrome was established by steroid investigations, operative or autopsy findings, or the response to therapy in each of the 111 patients. The probability calculations using only clinical and nonsteroid laboratory data led to a confident diagnosis ($p \geq 0.99$) in 9 of the 38 patients in whom the diagnosis of Cushing's syndrome was established. Of the 73 patients who did not have Cushing's syndrome the calculated probability of Cushing's syndrome was 0.01 or less in 45. In other words, in one half the patients suspected of Cushing's syndrome, the diagnosis could be confirmed or excluded with a high degree of confidence and with an accuracy far greater than that provided by simple steroid screening tests such as single plasma or 24-hr urine 17-hydroxycorticosteroid determinations. In the remaining patients, less certain and less accurate predictions of the diagnosis could be made. (*J Clin Endocr* **24:** 621, 1964)

IT HAS BEEN suggested that physicians could improve their utilization of clinical data in making diagnoses if they used probability theory in the analysis of diagnostic problems (1, 2). This report is an examination of an explicit method for estimating the probability of Cushing's syndrome in patients in whom this diagnosis is suspected, using clinical signs and simple laboratory techniques. In the traditional method for the differential diagnosis of endocrine disorders, the physician uses such data in addition to information gained from past experiences to make a decision concerning the probable diagnosis and the need for further investigation. He usually does not make an explicit formulation of either the information or the reasoning process leading to his decision. In the present report, the clinical and routine laboratory data from one group of patients investigated for Cushing's syndrome were examined to determine the incidence of the signs of the syndrome in the patients with and without the disorder. Using these data on the incidence of signs of the disorder together with Bayes' theorem, the probability of Cushing's syndrome was calculated for an additional group of patients investigated

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for suspected Cushing's syndrome. The probabilities so calculated were then compared with the final diagnoses established by specific steroid investigations, operative or autopsy findings, or by the response of the patients to therapy.

Methods

Patients were included in this analysis only if Cushing's syndrome had been suspected by the referring physician or if the possibility of hyperadrenocorticism was considered when the patient was seen in the clinic. The term Cushing's syndrome is applied to patients whose clinical findings are attributable to excessive cortisol production resulting from adrenal cortical hyperplasia, adenoma, or carcinoma.

In order to construct incidence tables on the frequency of Cushing's syndrome and the frequency of the signs of the disorder, the data from 211 patients investigated for suspected Cushing's syndrome were examined. The data on these patients were derived from 2 sources: a) patients examined in the Metabolic Clinic of the University of Utah and b) cases reported by Liddle from the Endocrine Clinic of the Vanderbilt University School of Medicine (3). The final diagnoses of these patients are shown in Table 1, A. Fourteen additional patients examined at Vanderbilt (3) and 3 examined at Utah were excluded from this report because a definite diagnosis could not be made on the basis of the steroid laboratory data. The laboratory methods used for identification of the patients with Cushing's syndrome are described elsewhere (3–7). Patients below the age of 5 or over the age of 65 and patients taking adrenal glucocorticoids were excluded.

The signs sought for in these patients were those previously reported (8) to occur in more than 10% of patients with Cushing's syndrome. In this presentation the term "signs" is applied to findings on physical or laboratory examination as well as to symptoms elicited in the history. In Table 2 are listed the 19 signs investigated, plus comments on their interpretation. All signs were graded as present (+), absent (0), or not examined or not appropriate (−). When a particular finding was minimal in degree or questionable it was graded 0. The term "not appropriate" was applied to oligomenorrhea in males and prepubertal or postmenopausal females, and to hirsutism in adult males. It should be noted that central and generalized obesity were interpreted as being mutually exclusive; that is, a patient might have one or the other or neither, but not both. If the patients were so massively obese that there was uncertainty whether or not central obesity was present, or when both generalized and central obesity seemed to be present, the patients were classified as having central obesity only. Several signs, although reported to occur with an increased incidence in Cushing's syndrome, were not used because they were difficult to identify or because information was available on too few of the patients. The serum potassium values of patients being treated with kaliuretic drugs were not used in this report.

Signs derived from quantitative measurements were separated into + and 0 in the following manner. A frequency distribution curve was constructed by plotting the proportion of individuals with Cushing's syndrome as a function of the measured variable. A separate curve was plotted for patients without Cushing's syndrome. The point at which the 2 distribution curves were estimated to cross was used to separate + from 0.

The data on the frequency of Cushing's syndrome and the incidence of the signs of the disorder derived from the above group of 211 patients were then used to calculate the probability of Cushing's syndrome for each of a second group of 111 patients. This second group of patients included: a) patients examined at the Endocrine Clinic of the Vanderbilt University School of Medicine since the earlier report by Liddle (3, and personal communication) and b) patients examined in the Metabolic Division of the Department of Medicine of Cornell University School of Medicine (R. E. Peterson, personal communication). The data on this second group of patients were obtained by examining their hospital records. The final diagnoses on these patients are shown in Table 1, B. With only a few exceptions, the patients in Table 1, A were observed over a period of from 3 to 10 years preceding this analysis, while those in Table 1, B had been observed more recently.

The probability of Cushing's syndrome being present in a particular case was calculated by using an expanded form of Bayes' theorem as derived by Warner *et al.* (2).

$$P(y_c/x_1, \bar{x}_2 \cdots x_j) = \frac{P(y_c)P(x_1/y_c)[1 - P(x_2/y_c)] \cdots P(x_j/y_c)}{\text{Numerator} + P(y_n)P(x_1/y_n)[1 - P(x_2/y_n)] \cdots P(x_j/y_n)} \cdot \quad \text{(Equation 1)}$$

In this equation, the expression on the left is the probability that a particular patient has Cushing's syndrome when certain signs, such as x_1, are present, and others, such as x_2, are absent. On the right $P(y_c)$ is the *a priori* probability that any patient referred with suspected Cushing's syndrome will have the syndrome; the incidence of the syndrome in the examined population in the past is used as an estimate of the value of $P(y_c)$. $P(x_1/y_c)$ is the probability of the occurrence of sign x_1 in y_c, *i.e.*, the incidence of the sign in patients with Cushing's syndrome. The term $[1-P(x_2/y_c)]$ is the probability of the absence of sign x_2 in y_c. The y_n terms refer to the patients without Cushing's syndrome. Signs which were not sought for in the examination or were not appropriate for the case are omitted from the calculations.

For speed and convenience in handling a large number of cases, all probability calculations in this report were performed with a digital computer. On individual cases these calculations can be performed with a desk calculator or estimated with pencil and paper.

Results

Of the 211 patients examined for incidence data (Table 1, A), 52 patients proved to have Cushing's syndrome. This provides an incidence figure for the syndrome of 0.25 in this series. The incidence of the signs selected for study in these patients is recorded in Table 3. The differences in the incidences of the signs between the patients with and those without Cushing's syndrome were examined by the use of the Chi square test (9). The incidences of the signs differed significantly from one another ($p < 0.05$) only in the case of signs 1–13 in Table 3. Therefore, only these signs were subjected to further analysis. Data on the volume of packed red cells (VPRC) were examined after corrections were made for the differences attributable to altitude (Salt Lake City, Utah—elevation 4360 feet; Nashville, Tennessee—elevation 450 feet); and sex (10). The details of this analysis are not presented here, since it did not improve the separation of the values for VPRC between patients with and without Cushing's syndrome.

Independence of the various signs of the syndrome is assumed in the expanded form of Bayes' theorem used in this report. The independence of the signs was examined separately in the case of those with and those without Cushing's syndrome. Two by two contingency tables were prepared for the actual and expected coincidences of the 154 possible paired combinations of the

TABLE 1. Final diagnoses on patients with suspected Cushing's syndrome*

Source	Cushing's syndrome	Not Cushing's syndrome
A. Patients used for incidence data on frequency of disease and frequency of signs		
Utah	17	94
Vanderbilt	35	65
	52	159
	Total: 211	
B. Patients used for calculating the probability of Cushing's syndrome		
Vanderbilt	13	56
Cornell	25	17
	38	73
	Total: 111	

* The relative frequency of patients with Cushing's syndrome in the early patients at Vanderbilt in A and in the patients at Cornell in B are not accurate reflections of the incidence of the disorder. At Vanderbilt the incidence of Cushing's syndrome among previously undiagnosed cases is about 19%, but included in the earlier group are known cases of the disorder which were sought out to test newly developed laboratory diagnostic methods (3). The extremely high incidence of Cushing's syndrome reported for Cornell in B is probably attributable to the fact that the present authors made no attempt at Cornell to assure equal sampling of charts on patients who proved to have and not have the disorder.

TABLE 2. Analyzed signs of Cushing's syndrome

Signs	Comments*
Osteoporosis	Considered present if x-ray films of the lateral thoracic or lumbar spine showed definite changes consistent with osteoporosis
Central obesity	Considered present when facial and trunkal obesity including high dorsal and supraclavicular fat pads were the major features of the obesity. Sign mutually exclusive with generalized obesity (see text for details)
Generalized obesity	Considered present if the patient was obese and the fat distribution was not preponderantly in the central portion of the body. Sign mutually exclusive with central obesity
Weakness	Defined as the inability to rise easily from a deep knee bend without the use of the arms. In the presence of extreme obesity or when the patients were older than 55, they were allowed minimal use of their arms for help in the maneuver without being considered weak
Ecchymoses and acne	Regarded as present only if found by the physician on physical examination. A single unexplained bruise up to 5 cm in diameter, and multiple bruises, if attributable to adequate trauma, were disregarded. Bruises on the legs of children were disregarded
Plethora	Interpreted to mean an abnormal diffuse purple or reddish color of the face
Red or purple striae	White striae were ignored
Edema	Present if the tissues could be pitted on pressure
Hirsutism	Present when there was definite increase in facial or body hair that was abnormal for the patient's age or sex
Oligomenorrhea and headache	The patient's complaint of these symptoms, if associated in time with the illness under consideration
Abnormal glucose tolerance	Fasting hyperglycemia or abnormally elevated blood sugar concentration 2 hr after 25 g of glucose intravenously or 3 hr after 100 g of glucose by mouth
Quantitated signs	These signs are: age 35 years or less, diastolic BP 105 mm Hg or above, serum potassium concentration 3.6 mEq/l or less, VPRC 49 or above, and white blood cell count 11,000 or more per mm^3

* The criteria used by Liddle in his earlier report differed from those in Table 2 only in that he considered weakness and ecchymoses to be present if a convincing history was obtained, and he did not require objective demonstration of the presence of these signs (3). At Utah only the objective findings of purpura or weakness were regarded as reliable, and only when these findings were present on physical examination were these signs recorded as present.

13 signs in the two groups of patients.[1] Only in the group of patients with Cushing's syndrome were significant associations ($p < 0.05$) found by the use of the Chi square test (9); these associated sign pairs were weakness and ecchymoses (signs 4 and 12, Table 3), weakness and low serum potassium (signs 4 and 13), edema and ecchymoses (signs 10 and 12), edema and low serum potassium (signs 10 and 13), and ecchymoses and low serum potassium (signs 12 and 13). Since sign 12 or 13 was involved in each of these combinations, these two signs were omitted to avoid including known dependent signs in Equation 1.

Although no association of the remain-

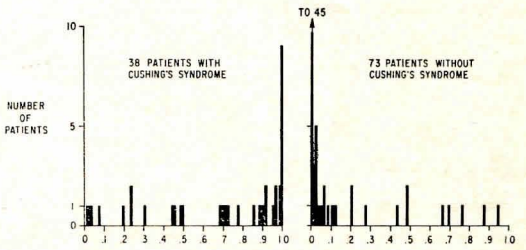

FIG. 1. Number of individuals with Cushing's syndrome (left) and without Cushing's syndrome (right) plotted as a function of the probability of Cushing's syndrome when certain signs were present. The calculations were performed by using Equation 1 and the data of signs 1–11 of Table 3.

[1] In the case of the mutually exclusive signs, generalized obesity and central obesity, there was no coincidence by definition and no tests for association were performed. Analyses for combinations of signs greater than 2 in number were not done; this approach did not seem warranted in view of the large number of possible combinations and the relatively small number of cases in this study.

TABLE 3. Incidence of the signs of Cushing's syndrome among 211 patients in whom this syndrome was suspected

	Patients with Cushing's syndrome	Patients without Cushing's syndrome
1. Osteoporosis*	0.64	0.03
2. Central obesity	0.90	0.29
3. Generalized obesity	0.03	0.62
4. Weakness	0.65	0.07
5. Plethora	0.82	0.31
6. WBC 11,000 per mm^3 or more	0.58	0.30
7. Acne	0.52	0.24
8. Striae (red or purple)	0.46	0.22
9. Diastolic BP 105 or above	0.39	0.17
10. Edema (pitting)	0.38	0.17
11. Hirsutism	0.50	0.29
12. Ecchymoses	0.53	0.06
13. Serum K 3.6 mEq/l or less	0.25	0.04
14. Oligomenorrhea	0.72	0.51
15. Headaches	0.41	0.37
16. VPRC 49 or above	0.37	0.32
17. Females	0.65	0.77
18. Abnormal GTT	0.88	0.77
19. Age 35 or less	0.55	0.52

* The only notable difference in the incidence of signs between that recorded in this table and that actually found in the 111 patients used for probability calculations was in regard to osteoporosis, the incidence of which was 0.26 and 0.06, respectively, in the patients with and without Cushing's syndrome. This change is attributable probably to earlier diagnosis of the more recently examined patients with Cushing's syndrome. For future probability calculations these more recent figures on the incidence of osteoporosis should be used in place of those given in the table.

ing 11 signs with one another was identified by the Chi square analysis, this does not prove that they are independent. In order to further examine the question of independence of the remaining signs, the contingency coefficient (C) which has a range of 0 to 0.707 was calculated for each pair of signs (11). Of 108 pairs of signs in the two groups of patients, only three had an absolute value for C greater than 0.3 and none was greater than 0.4. These uncommon associations may well be attributable to chance. Thus, for this study, independence of signs 1 to 11 is assumed, but it is recognized that with the acquisition of additional data this assumption may have to be modified.

The first 11 signs in Table 3 were used in Equation 1 in calculating the probability of Cushing's syndrome in the additional group of 111 patients examined for suspected Cushing's syndrome (Table 1, B). At least 85% of these patients were examined for each of signs 1 to 3 and 5 to 11. Only 40% of the patients were examined for the valuable sign of objective evidence of weakness (sign 4). The results of the probability calculations on the 111 patients are shown in Fig. 1 and are summarized in Table 4. The probability calculations led to a confident diagnosis ($p \geq 0.99$) in nine of the 38 of these patients in whom the diagnosis of Cushing's syndrome was established. Of the 73 patients who did not have Cushing's syndrome the calculated probability of Cushing's syndrome was 0.01 or less in 45. In the cases in which the clinical data strongly favored one or the other diagnosis, that is, in 54 of 111, no diagnostic errors were made. In one quarter of the cases, 27/111, the calculated probabili-

TABLE 4. Results of probability calculations

Calculated probability values	Likelihood of Cushing's syndrome	No. of patients	
		Cushing's syndrome	Not Cushing's syndrome
.01 or less	Very unlikely	0	45
between .01 and .1	Unlikely	4	14
from .1 to .9	Uncertain	17	13
between .9 and .99	Likely	8	1
.99 or more	Very likely	9	0
		38	73

ties ranged from 0.01 to 0.1 and from 0.9 to 0.99 and the differential diagnosis could be made with less confidence. In this group five of the 27 diagnoses were incorrect. In the remaining quarter of the cases (30/111), the probabilities ranged from 0.1 to 0.9 and the calculations were not valuable in the evaluation of the patients.

Discussion

An attempt has been made in this report to increase the diagnostic usefulness of information derived from simple clinical and laboratory data normally collected on the first endocrine clinic visit of patients suspected of having Cushing's syndrome. Past difficulties with clinical diagnoses usually lead physicians to adopt a cautious attitude toward making a definite diagnosis of Cushing's syndrome on clinical grounds alone. Actually, using only clinical and nonsteroid laboratory data, it was possible to make a confident diagnosis in half the patients. In this group, when the diagnosis of Cushing's syndrome was either very likely or very unlikely, simple steroid screening tests such as single plasma (5, 6) or 24-hour urine (3) 17-hydroxycorticosteroid determinations are much less reliable than the calculated probability based on the nonsteroid data and are not needed. Because major surgery or irradiation must be considered in those patients with a high calculated probability of Cushing's syndrome, critical tests such as adrenal suppression or the determination of cortisol production are desirable to increase the probability of the diagnosis by another order of magnitude before recommending definitive therapy. In the other half of the patients, in whom less confident diagnoses could be established on the basis of the clinical and nonsteroid laboratory data, a steroid screening procedure is indicated.

Local conditions relating to the source of referred patients and the interpretation of the signs in Table 2 will determine the incidence of the disorder and its signs at other endocrine clinics.[2] The physician in an established endocrine clinic may prefer to determine the incidence of the disorder and its signs by an analysis of his own experience. If this information is not available, the incidence data used in this report may be taken as estimates. Both in the method used in this report and in clinical diagnosis as usually practiced there are signs like central obesity which are difficult to define and whose use involves a large subjective element. Our experience with this method of calculating the probability of Cushing's syndrome emphasizes the need for more objective criteria in the identification of clinical signs.

The data recorded in Fig. 1 suggest that clinically it is easier to confidently exclude the diagnosis in patients suspected of having Cushing's syndrome than to identify patients with the syndrome. In the future, if patients are examined for all of signs 1 to 11 in Table 3, and particularly for the presence or absence of weakness, as shown by impaired ability to rise from a deep knee bend, a greater accuracy in the diagnostic predictions can be expected. There are, of course, additional valuable signs used by some physicians in the identification of patients with Cushing's syndrome, which, if added to the first 11 signs in Table 3, might increase the accuracy of the predictions. For example,

[2] The following is an example of the influence of the incidence of the disorder on its calculated probability. If a patient had an estimated probability of Cushing's syndrome of 0.9, as calculated using the incidence rate of this report for Cushing's syndrome among patients suspected of the disorder (0.25), the calculated probability would change to 0.75 if the incidence of the disorder were only 0.1.

two of the 17 patients with Cushing's syndrome at Utah had skin which was easily lacerated. In these two patients, mild trauma at times caused a laceration which bled extensively and required surgical suturing or skin grafts. The trauma in one case consisted of the removal of adhesive tape. This sign might be termed "ripped skin." The possible value of this sign was called to our attention by Dr. G. W. Liddle, who has observed it in a similar incidence in his larger series of patients with Cushing's syndrome. It is also our impression that the red or purple striae in Cushing's syndrome are frequently 1 cm or more wide, while the similarly colored striae seen in some obese patients without adrenal disease are usually narrower. It might be helpful to differentiate between wide and narrow striae in the future, but we have no quantitative data on this point at present.

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