during the week after methylprednisolone treatment but no change occurred in another patient (case 5), who responded extremely well to treatment. It is impossible to draw conclusions from such small numbers about the possible pathogenic relevance of this antibody.

Now that intravenous methylprednisolone has been shown to be effective the therapeutic schedule needs to be optimised. A modest maintenance dose of oral steroid appeared to be necessary from our preliminary findings in two patients, who after a good response to intravenous methylprednisolone began oral prednisolone 10 mg daily but within a week had reverted to their pretreatment state. We may have been overcautious with the dose of methylprednisolone and possibly repeated doses of methylprednisolone might be preferable. This would best be investigated in a multicentre trial.

In conclusion, intravenous methylprednisolone appears to be an important new approach to the management of Graves' ophthalmopathy. It is probably preferable to other means of treatment for patients with severe disease, and is certainly preferable to very high dose oral prednisolone, giving a better response with fewer adverse effects. Idiosyncratic cardiovascular deaths have been reported and patients should be assessed medically before treatment; for this reason it should be reserved for patients with visual impairment. The rapid response is a useful feature and patients whose visual acuity does not improve after 48 hours may be referred early for surgery. Though numbers in our series were small, we emphasise that the patients who failed to respond were those with the longest history. This agrees with previous studies using other modes of treatment.[15 16] The implication is that patients with Graves' ophthalmopathy should be referred as early as possible to a specialist centre.

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Looking for gall bladder disease in the patient's iris

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Abstract

In alternative health care iridology is used as a diagnostic aid. The diagnosis of gall bladder disease was used to study its validity and interperformer consistency. The presence of an inflamed gall bladder containing gall stones is said to be easily recognised by certain signs in the lower lateral part of the iris of the right eye. Stereo colour slides were made of the right eye of 39 patients with this disease and 39 control subjects of the same sex and age. The slides were presented in a random order to five leading iridologists without supplementary information. The prevalence of the disease was estimated at 56%. The median validity was 51% with 54% sensitivity and 52% specificity. These results were close to chance validity (iota=0·03). None of the iridologists reached a high validity. The median interperformer consistency was 60%. This was only slightly higher than chance consistency ($\varkappa$=0·18).

This study showed that iridology is not a useful diagnostic aid.

Introduction

Many parts of the human body are projected in the brain.[1] Some people believe that projection also exists in other organs—for example, the tongue, feet, ears.[2] In 1881 von Péczely wrote a book on diagnosis using the eye, in which he gave a schematic representation of the topography of the organs in the iris. Some people now believe that many diseases manifest themselves in the iris,[3] which is supposed to indicate not only the existence of certain diseases but also the tendency for their development ("constitution"). Iridology is practised on a large scale especially in alternative medicine, in which it is considered to be an important diagnostic supplement to the medical history and (conventional) physical examination.

The emphasis of this study was on the validity of iridology and on consistency among iridologists. Because using iridology is doubted on both theoretical and empirical grounds[3 4] I chose a simple test: to study patients with an obvious disease that according to iridologists cannot be overlooked—namely gall stones

in an inflamed gall bladder (gall bladder disease)—and healthy controls.[5] According to textbooks, the gall bladder is projected in the lower lateral part of the right iris. Gall stones may induce small, dark spots there while the accompanying inflammation is recognised as white lines.[3] I tested to what extent skilled iridologists could distinguish between people with and without gall bladder disease and the consistency among these iridologists.

Patients and methods

The study was a blinded case-control study.[5] The 39 patients (14 men and 25 women) were a consecutive series from the Academic Hospital in Maastricht who were to have their gall bladder removed the next day. Patients with jaundice or without inflammation were excluded from the study. The presence of gall stones and inflammation was confirmed afterwards by chemical and histological examinations.

A control group of the same size, matched closely for sex and age, was recruited from patients at the same hospital with other, unrelated diseases. This group also included healthy volunteers. None had ever had an operation for gall bladder disease or had a history or symptoms of gall stones. Furthermore, patients with silent gall stones were excluded by means of ultrasound. None of the controls had jaundiced eyes.

Stereo colour slides were made of the right iris of all 78 subjects. Those of the patients with gall bladder disease were made the day before the operation. The slides showed the eye at its actual size. Studying the slides with a stereo magnifier gave a three dimensional image. This is a common procedure among iridologists.

Five iridologists (A-E) were chosen, of whom two were medical doctors (B and E). All five had used iridology in their practice for many years and were leaders in their specialty. They willingly took part in the study. They were sent test slides before the study and considered them to be appropriate. The reviewers were told only the sex and age of each subject and that some of them had gall bladder disease. No information was given about the medical history or results of physical or other investigations.

The slides were coded and arranged in random order. Copies were sent to each reviewer, who then scored each patient for the probability of gall bladder disease: definite (95%), probable (80%), possible (65%), do not know (50%), possibly not (35%), probably not (20%), definitely not (5%). The data were processed and analysed. The observed validity of iridology was expressed as its sensitivity and specificity.[6] To take chance validity into account iotas were also calculated (see appendix). I also drew receiver operating characteristic curves. The observed consistency was computed for every pair of iridologists, and kappas were calculated to take chance consistency into account.[7]

VALIDITY

All five reviewers completed the study. They did not consult each other about the interpretation of slides. One iridologist (E), however, was helped by a paranormal healer. Table I shows the scores of the five iridologists. Only 21 of the 390 assessments (5%) were scored as "do not know," of which 15 were marked so by one iridologist (C). These 21 assessments were not included in the other calculations in table I. All scores ≥65% (possible, probable, and definite gall bladder disease) were considered to be positive results and all scores ≤35% negative. The iridologists estimated the prevalence of gall bladder disease in all the subjects to be 56% (range 47-59%), which was close to the real prevalence in the study.

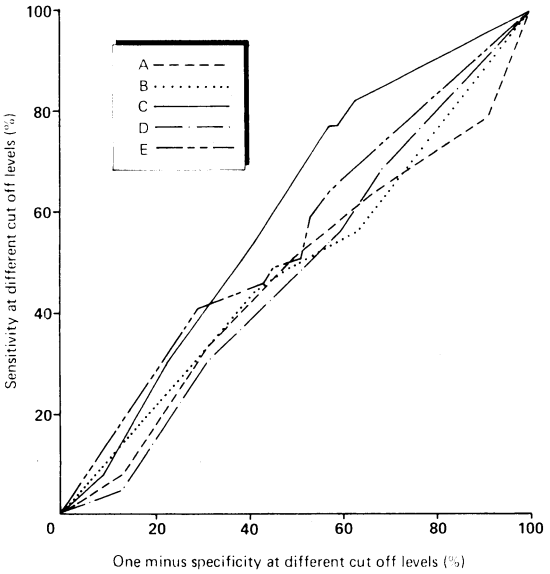
The median observed validity was 51% (range 47-60%). When the prevalence or the estimated prevalence is close to 50% roughly half of the subjects will have correct test results by chance. Iota ranged from −0·05 to 0·21 with a median of 0·03. This indicated almost zero validity. The validity of a diagnostic test is usually expressed as its sensitivity and specificity. The median sensitivity was 54% (range 49-70%), which was close to the chance sensitivity—that is, the estimated prevalence. Iota for the sensitivity ranged from −0·06 to 0·27 with a median of 0·02. This indicated almost zero sensitivity with many false negative diagnoses. The median specificity was 52% (range 41-54%), which was close to the chance specificity—that is, one minus the estimated prevalence. Iota for the specificity ranged from −0·05 to 0·17 with a median of 0·03. This indicated almost zero specificity with many false positive diagnoses.

For 15 subjects at least four iridologists considered the iris image to be negative for gall bladder disease. Among these subjects seven had gall stones in an inflamed gall bladder. For 20 subjects at least four iridologists considered the iris image to be positive. Among these subjects 10 had no history or symptoms of gall bladder disease and their ultrasound examination yielded negative results.

The cut off point above and below which a diagnostic test can be considered to be positive and negative is arbitrary to a certain extent. Originally probabilities of gall bladder disease of ≥65% and ≤35% were chosen as cut offs. When more stringent cut offs were chosen the results remained the same—for instance, at cut offs of ≥80% and ≤20% the observed validity, sensitivity, and specificity were all close to 50%, which is low at an estimated prevalence of 50%. Iotas ranged from −0·03 to 0·22 with medians of zero. The choice of two different cut offs means that data in between are excluded from the analysis. With one cut off the data can be depicted in a receiver operating characteristic curve. The figure shows the relation between the sensitivity and one minus the specificity at various cut offs. The curve for each of the five iridologists was close

TABLE I—*Numbers of patients assessed by five iridologists (A-E) as being positive or negative for gall bladder disease. For prevalence, estimated prevalence, observed validity, sensitivity, and specificity cut offs were ≥65% and ≤35% probability*

	A		B		C		D		E	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Iridologists' assessment of probability:										
95%	3	5	17	16	3	3	2	5	16	11
80%	10	7	2	3	9	6	10	7	2	6
65%	6	6	2	4	9	7	9	10	1	
50%					9	6	1	1	1	3
35%	6	8	1	1		1	5	4	3	
20%	6	9			2	1	12	12	2	2
5%	8	4	17	15	7	15			14	17
Prevalence	0·50		0·50		0·48		0·50		0·51	
Estimated prevalence	0·47		0·56		0·59		0·57		0·49	
Validity (iota)	0·51 (0·03)		0·47 (−0·05)		0·60 (0·21)		0·49 (−0·03)		0·51 (0·03)	
Sensitivity (iota)	0·49 (0·02)		0·54 (−0·06)		0·70 (0·27)		0·55 (−0·03)		0·50 (0·03)	
Specificity (iota)	0·54 (0·03)		0·41 (−0·05)		0·52 (0·17)		0·42 (−0·02)		0·53 (0·03)	



Receiver operating characteristic curve for five iridologists in their diagnosis of gall bladder disease

to the diagonal. So at every cut off the sensitivity approximated one minus the specificity, which indicated likelihood ratios of unity.

CONSISTENCY AMONG THE REVIEWERS

Although I found that the iridologists could not distinguish between cases and controls, the question remained as to what extent they agreed with each other on the diagnoses. I chose cut offs of ≥65% and ≤35% probability of gall bladder disease. I then examined the scores of every pair of iridologists for their consistency on positive and negative results. Table II shows the data for every pair of reviewers, after exclusion of inconclusive scores, and the observed consistency and kappa. The observed consistency ranged from 47% to 64% with a median of 60%. This was not high as the chance consistency is roughly 50% if one of the estimated prevalences is close to 50%. Kappa ranged from −0·06 to 0·28 with a median of 0·18. At more stringent cut offs the results remained the same—for instance, at the cut offs ≥80% and ≤20% probability the median observed consistency was 60% (range 46-67%) with a chance consistency of 50%. Kappa ranged from −0·08 to 0·33 with a median of 0·17.

Because quantitative test scores were available quadratically weighted kappas could also be calculated. As the square of differences between the scores of the reviewers were included in the kappa formula the many strong disagreements led to a low kappa. This kappa varied among the 10 comparisons from −0·07 to 0·26 with a median of 0·17.

TABLE II—*Consistency among five iridologists (A-E) in their diagnosis of gall bladder disease. Upper right shows data for every pair of iridologists*; lower left gives observed consistency (κ)*

	A	B	C	D	E
A		25 12 19 22	22 8 15 18	23 14 20 19	16 19 20 19
B	0·60 (0·21)		24 12 13 14	29 13 14 20	22 19 14 19
C	0·63 (0·28)	0·60 (0·19)		23 13 12 14	17 17 12 14
D	0·55 (0·11)	0·64 (0·28)	0·60 (0·18)		24 17 11 21
E	0·47 (−0·06)	0·55 (0·11)	0·52 (0·04)	0·62 (0·24)	

*Key to box showing data for pair of iridologists X and Y:

X \ Y	+	−
+	+ +	+ −
−	− +	− −

Discussion

For people who believe in iridology as an important diagnostic aid for gall bladder disease my results must be disappointing. Even among leading iridologists iridology does not seem to be a valid diagnostic test, and the consistency among the reviewers was low. I focused on gall bladder disease because, firstly, it was suggested by the iridologists themselves and one of them stated, "Inflammations are easy to see. Kidney stones and gallstones even more so"[8]; secondly, gall bladder disease is common; and, thirdly, it can be diagnosed fairly straightforwardly. Nevertheless, an occasional patient with a silent gall stone in the control group may have been overlooked. The chance, however, that the control group included one or more patients with gall stones in an inflamed gall bladder was small. The observed specificity was only 52%, which is close to one minus the estimated prevalence of gall bladder disease among all 78 subjects. Proponents of iridology might argue that half of the control group was free from gall bladder disease but might have the "constitution" for its development in the future. Iridology would then maintain its validity in estimating the predisposition.

This reasoning is not convincing when the sensitivity is also considered. All of the cases studied were of gall stones in an inflamed gall bladder, but the observed sensitivity was only 54%, which is close to the estimated prevalence of gall bladder disease among all 78 subjects. Any claim that the predisposition was already expressed in the iris is untenable, bearing in mind the many false negative scores among the patients with gall bladder disease.

There is only one explanation for the low validity of the reviewers: iridology is not a valid test for diagnosing gall bladder disease. Other studies have been carried out on iridology, and most of them were summarised by Dern.[3] Many are not particularly informative as the reviewers weren't particularly skilled and blinding was not done. Studies done by unskilled reviewers who did not believe in iridology tended to have negative results. Believers in iridology sometimes reached a high percentage of correct diagnoses, expecially when they had known about the patients beforehand. Simon *et al* evaluated the validity of iridology for kidney problems and found similar results to those of my study.[9]

I also examined consistency among the reviewers. The consistency between two iridologists in their diagnosis was 60%, which was only slightly higher than chance consistency. This strengthened the impression that iridology is not a useful diagnostic aid.

I sent this report to the iridologists who participated in the study. They were disappointed with the results and commented that (*a*) evaluating the image of the iris without access to other medical information is difficult; (*b*) assessments are more easily made with slides of both irises of the patient; (*c*) possibly other diseases apart from gall bladder disease are manifested more clearly in the iris; and (*d*) the conclusion was too final.

I thank the patients and controls for their participation in the study, the iridologists, and the many other people who helped.

APPENDIX: IOTA FOR DIAGNOSTIC VALIDITY

The diagnostic quality of a reviewer must be evaluated in relation to the proportion of the patients who are considered to have a positive test result—that is, to the estimated prevalence (EP). When no gold standard is present two reviewers, A and B, can be studied for their consistency. The observed consistency (OC) must be compared with the chance consistency (CC), where $CC=(EP_A)(EP_B)+(1-EP_A)(1-EP_B)$. The consistency among reviewers is commonly expressed as Cohen's kappa (κ), which is defined as (OC−CC):(1−CC).

$\varkappa=1$ indicates perfect consistency and $\varkappa\leq 0$ complete inconsistency.

When a gold standard is present the validity of every reviewer can be studied. The observed validity (OV)—that is, the proportion of correct diagnoses—must be compared with the chance validity (CV), where CV=(EP)(P)+(1−EP)(1−P) and P is the real prevalence. When EP=P, CV=$2(EP-0{\cdot}5)^2+0{\cdot}5$.

A simple overall measure for diagnostic validity is (OV−CV):(1−CV). Because validity is more important than consistency it is named iota (I), one letter before kappa in the Greek alphabet. Iota among patients with disease is I(sensitivity)=(OSE−EP):(1−EP), in which OSE stands for the observed sensitivity. Iota among those without disease is I(specificity)=(OSP−(1−EP)):(1−(1−EP)), in which OSP stands for the observed specificity. I=1 indicates perfect validity and I≤0 no validity at all beyond chance validity.

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Aluminium accumulation and immunosuppressive effect in recipients of kidney transplants

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Abstract

Aluminium that has accumulated in the body is thought to have a generalised cytotoxic effect. A prospective study of aluminium accumulation in bone—that is, subclinical aluminium toxicity—was carried out in 94 recipients of kidney allografts, who were followed up for three years. Subclinical aluminium toxicity was found in 66 patients. A significantly smaller proportion of patients with aluminium accumulation experienced a rejection episode: 30 (58%) *v* 12 (86%) who received grafts from cadavers and 4 (29%) *v* 10 (71%) who received grafts from living donors. On multivariate analysis only the source of the kidney and aluminium accumulation were found to influence the rejection rate.

These findings suggest that aluminium accumulation has an immunosuppressive effect.

Introduction

Aluminium accumulation is a potential hazard of end stage chronic renal failure.[1,2] Aluminium toxicity is indicated by the accumulation of aluminium in bone and by symptoms and signs from several organs.[3,4] The biochemical basis of aluminium toxicity is complex,[5] but the diverse clinical pictures suggest a generalised cytotoxic effect.[4] Its influence on immune function remains to be elucidated. We report a prospective study of aluminium accumulation in recipients of kidney transplants and its relation to immune events after transplantation.

Patients and methods

We studied 94 adult patients, who gave their informed consent to participate and received a kidney graft from a cadaver (n=66) or a living donor identical for histocompatibility antigens (n=28) during one year (1983-4). They represented 83% of all patients eligible for study. Patients who received a cadaveric transplant were selected on the basis of medical urgency, waiting time, and a negative result of a cross matching test against donor T cells. Blood transfusions were given for medical reasons only. The patients' immune systems were suppressed by a uniform regimen that included cyclosporin and steroids.[6] Rejection episodes were treated by intravenous bolus doses of methylprednisolone.[6] All patients were followed up for three years.

Rejection episodes were defined by a rise in serum creatinine concentration not explained by non-immunological complications as shown by renography, sonography, computed tomography, monitoring of cyclosporin concentrations, and intravenous pyelography or angiography; improved renal function after treatment for rejection; or results of renal biopsy. Non-functioning grafts were monitored by fine needle aspiration cytology.

Randomly chosen sections of a specimen of transiliac bone obtained during the transplant operation were stained with aurin tricarboxylic acid and Prussian blue. Aluminium accumulation was said to be present if the aurin tricarboxylic acid stain was positive[7] and the Prussian blue stain negative. Histochemical staining for aluminium is usually negative unless the aluminium content in bone exceeds 50 mg/kg dry weight (10 times the normal concentration).[8]

Wilcoxon two sample tests and Fisher's exact tests were used to test differences between groups. One sided Fisher's exact tests were used as aluminium is known to have toxic effects only in biological systems. Log rank tests were used to test differences in survival rates. Multivariate analyses were performed to test simultaneously the influence on the rejection rate of several factors existing before transplantation. This was done with a logistic model and generalised linear interactive modelling[9]—that is, a logit analysis as all covariates were categorised.

Results

Aluminium accumulation was found in 52 (79%) patients who received kidneys from cadavers and 14 (50%) patients who received kidneys from living donors (table I). Age, histocompatibility matching, and the proportion of patients previously given transfusions or dialysis were similar in patients positive and negative for aluminium.

One and three year survival rates of patients were 89% and 76% for recipients of kidneys from cadavers and 100% for recipients of kidneys from living donors, with no difference between groups of patients positive and negative for aluminium. One and three year survival rates of grafts were 73% and 62% for kidneys from cadavers and 96% and 82% for kidneys from living donors. Patients positive for aluminium tended to have better graft survival than patients negative for aluminium, but the difference was not significant.

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