A Novel Approach to the Detection of Acromegaly: Accuracy of Diagnosis by Automatic Face Classification

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Context: The delay between onset of first symptoms and diagnosis of the acromegaly is 6–10 yr. Acromegaly causes typical changes of the face that might be recognized by face classification software.

Objective: The objective of the study was to assess classification accuracy of acromegaly by face-classification software.

Design: This was a diagnostic study.

Setting: The study was conducted in specialized care.

Participants: Participants in the study included 57 patients with acromegaly (29 women, 28 men) and 60 sex- and age-matched controls.

Interventions: We took frontal and side photographs of the faces and grouped patients into subjects with mild, moderate, and severe facial features of acromegaly by overall impression. We then analyzed all pictures using computerized similarity analysis based on Gabor jets and geometry functions. We used the leave-one-out cross-validation method to classify subjects by the software. Additionally, all subjects were classified by visual impression by three acromegaly experts and three general internists.

Main Outcome Measure: Classification accuracy by software, experts, and internists was measured.

Findings: The software correctly classified 71.9% of patients and 91.5% of controls. Classification accuracy for patients by visual analysis was 63.2 and 42.1% by experts and general internists, respectively. Classification accuracy for controls was 80.8 and 87.0% by experts and internists, respectively. The highest differences in accuracy between software and experts and internists were present for patients with mild acromegaly.

Conclusions: Acromegaly can be detected by computer software using photographs of the face. Classification accuracy by software is higher than by medical experts or general internists, particularly in patients with mild features of acromegaly. This is a promising tool to help detecting acromegaly. **(*J Clin Endocrinol Metab* 96: 2074–2080, 2011)**

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Abbreviation: 2D, Two-dimensional.

Acromegaly is a rare disease caused by GH excess, which in most cases is due to a pituitary adenoma. Acromegaly is accompanied by organomegaly, metabolic deterioration, multimorbidity, and increased mortality (1, 2). The onset of the disease is slow, and the delay from the onset of first symptoms to diagnosis is 6–10 yr (3, 4). Although efforts have been made to recognize acromegaly earlier and diagnostic tests have improved, the delay from onset of symptoms to diagnosis of the disease has not changed in the last 3 decades (4). An early detection of acromegaly is desirable because it would increase the likelihood of preventing irreversible complications of GH excess.

Patients with acromegaly present with enlargement of hands and feet and typical changes of the face including enlargement of nose, jaw, forehead, and cheekbones. Therefore, we aimed to test whether a computerized face classification system helps diagnosing acromegaly. Previous studies have shown that face classification software using regular two-dimensional (2D) photographs allow distinguishing between different genetic syndromes (5–7).

An attempt has been made to recognize acromegaly by a computer program using a morphable model that establishes a three-dimensional model from a regular 2D photograph (8). However, only a very limited number of patients was included in this study, patients and controls were not matched by age and sex, there were differences in sex and ethnic background between patients and controls, and the photographs from patients and controls were not taken under the same conditions, thus allowing for potential systematic error.

We hypothesized that face classification software that analyzes regular 2D frontal and side photographs of the face is able to distinguish between subjects with and without acromegaly better than general practitioners as well as endocrinologists who are familiar with acromegaly.

Subjects and Methods

Patients and controls

The study was approved by the Ethics Committee of the Ludwig Maximilians University Munich and conforms to the Declaration of Helsinki. All participants gave written informed consent. All patients whose pictures are shown here gave separate informed consent for showing their pictures. We recruited patients with acromegaly from the endocrine outpatient clinics of the Medical Hospital Innenstadt, University Hospital, and the Max Planck Institute of Psychiatry (Munich). Additionally three patients were included during a patient information event for patients with pituitary diseases at the Max Planck Institute of Psychiatry.

In total we included 57 patients with acromegaly (29 women, mean age ± SD 58.7 ± 14.0 yr, GH 5.2 ± 14.0 μg/liter, IGF-I 267 ± 245 μg/liter; 28 men, 51.4 ± 13.1 yr, GH 2.7 ± 3.4 μg/liter, IGF-I 312 ± 204 μg/liter). In all patients acromegaly had been proven by nonsuppressed GH in an oral glucose tolerance test and IGF-I levels above the age- and sex-specific reference range as recommended in current guidelines (9). At the time of the photography, acromegaly was biochemically controlled in 29 patients (17 of 29 women, 12 of 25 men) as defined by presence of normal IGF-I levels. Data on IGF-I and biochemical control were missing in two patients who were recruited from the patient information event. Thus, data on biochemical control were available in only 55 patients.

Controls were recruited from volunteers at the Medical Hospital Munich and patients from the outpatient clinics of both institutions. We did not include subjects as controls if they had GH excess or deficiency, overt hyper- or hypothyroidism, Cushing's syndrome, glucocorticoid treatment other than replacement, or consuming diseases. Controls were matched by sex and age to the patients. We included 59 controls (29 women 55.2 ± 12.5 yr, $P = 0.32$ *vs.* female patients; 30 men, 51.7 ± 17.0 yr, $P = 0.97$ *vs.* male patients; pathologies, n = 12 no disease, n = 23 biochemically controlled thyroid disease, n = 6 pituitary disease, n = 4 pulmonary disease, n = 4 type 2 diabetes, n = 3 type 1 diabetes, n = 3 hypertension, n = 2 adrenal disease, n = 1 carcinoid with stable disease, n = 1 parathyroid disease, n = 1 nycturia). All patients and controls were Caucasians.

Photographs

Frontal and side views were taken with the subjects standing in front of a white wall with a digital camera. At the beginning of the study, pictures were taken with a compact digital camera (Ixus 70; Canon, Tokyo, Japan) that was used on the first 14 patients without flash light and under diffuse light to avoid shading. For the following patients and controls, we used a consumer-level DSLR camera (Canon EOS 450d with Canon EF-S 18–55 mm IS) to provide for greater sharpness, reduced image noise, and reduced barrel distortion. The process was standardized by using constant camera settings (focal length 28 mm, f5.6, ISO 400, exposure time 1/60 sec) and activating the built-in camera flash for homogenous illumination, a white wall was used as a background. To check whether different cameras and settings might introduce bias, we additionally photographed four controls and six patients with both cameras and settings and compared outcomes. One picture was selected for each view type and then cropped and rescaled to show the same image section throughout. All subjects were asked to take a neutral facial expression without smiling and to take off glasses.

Face classification

Before face classification, we grouped all acromegalics into subjects with mild, moderate, or severe facial features of acromegaly by overall impression. Grouping was performed independently by physicians with extensive experience with acromegaly (H.J.S. and J.R.) by viewing the frontal and side views of the photographs. In case of discrepancy, a third physician (J.S.) decided on the final grouping.

Face classification was performed with the software tool FIDA (facial image diagnostic aid) with a method developed for the recognition of face identity as described previously (10) and developed further later on by M.G. and R.P.W. at the Ruhr-University of Bochum (copyrights remain with them). It runs on a standard personal computer under Windows (7 or XP; Mi-

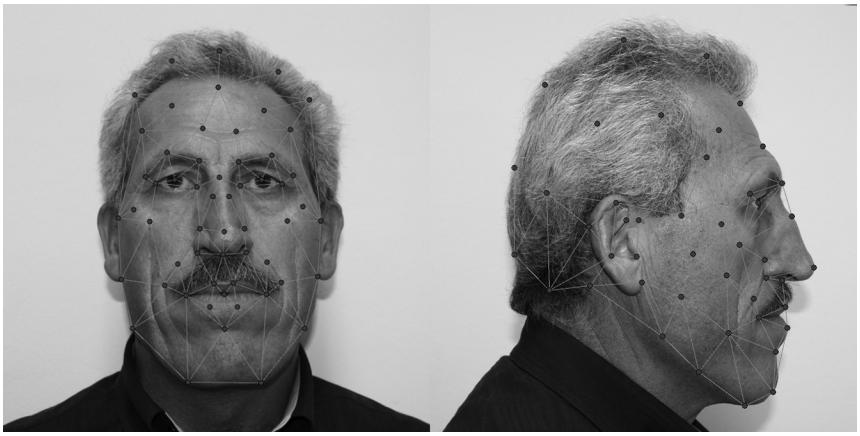

FIG. 1. Example of labeling. The first two faces were labeled by hand on prespecified landmarks. Afterward face detection and labeling was performed automatically using modified elastic bunch graph matching. Face recognition was performed by applying two principles and combinations of both: analysis of texture by analyzing Gabor jets beneath the nodes and geometry by analyzing edge length and distances between the nodes.

crosoft, Richmond, CA), requires a Java virtual machine and approximately 1 GB of RAM and disk space, respectively. It supports creating a face database with diagnostic annotations and manual postprocessing. After the database has been built, classifications are provided for novel images. The software has provisions for sharing face data securely between research groups to arrive at more extensive databases. Consequently, the pure software without any patient data is available from the authors on request and free of charge for scientific purposes.

Initially the frontal and side views of the first two faces were labeled with graphs of 57 and 46 nodes, respectively, and edges connecting the nodes. Nodes were placed on prespecified facial landmarks expected to be relevant for the discrimination of acromegaly from controls as shown in Fig. 1. The faces included thereafter were detected by the software using modified elastic bunch graph matching, and the nodes were placed automatically (5, 10). Afterward the node positions were edited manually to exactly fit to the initially chosen landmarks in the face. We found that with increasing size of the database, automatic detection became more accurate. However, manual editing was still necessary in the complete database. The pictures were automatically downsampled to a resolution of 168 × 224 pixels. To establish a training set, all included subjects were manually classified as patients or controls.

The face classification software applied two principles to compare graphs for similarity: texture and geometry. For the analysis of texture, Gabor jets beneath the nodes were analyzed using different algorithms for similarity functions (10). A Gabor jet is a feature vector into which the responses of different Gabor wavelets at a specific position in the image are arranged. The principles and the application of this technique in syndrome classification have been described previously (5–7). For the analysis of geometry, different combinations of edge length and node distances were compared.

In total, we tested five different functions based on Gabor jets [A (scalar product); P (scalar product including phase); C (Canberra similarity); M (modified Manhattan similarity); and D (disparity similarity)] and four different functions based on geometry [E (edge length difference); L (edge difference length); H (edge vector difference); N (node position distance)], and combinations of both principles. All functions were tested on frontal and side views of patients and controls. Details are given in the online appendix, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

For classification of subjects by the software, we used the leave-one-out cross-validation method. The classifier was trained on all faces except one by learning the statistics of texture and geometry similarity values. The remaining face was then classified by the software using texture and geometry as described above and combinations of both. This procedure was repeated until all faces were classified by the software. The classifier compares new faces to the averages of all acromegalics and all controls, respectively, in the training set and yields a similarity to each class. The new face is grouped into the class with the higher similarity value. The class similarities can be interpreted as probabilities of class membership. Therefore, the software can, in principle, be used to evaluate the time course of images of the same patient over the years. This is, however, far beyond the range of the current study.

Additionally, we presented the same photographs to three experts (two endocrinologists and a neurosurgeon) with extensive experience in acromegaly (J. Honegger, C. Schöfl, C. Strasburger) and to three general internists who were not particularly familiar with acromegaly (B. Hempfling, W. Hempfling, S. Böhlandt). From each patient and control subject, a picture showing a frontal and a side view was presented for 12 sec in a random order to each expert and internist. The experts and internists were asked to classify all 116 presented subjects as acromegalic or nonacromegalic by their impression of the pictures. They were not told how many acromegalic patients were contained in the database.

Statistical analyses

Descriptive analyses were done using means and SD. We calculated accuracy of classification and sensitivities and specificities. We compared means using Student's *t* test. A two-sided $P = 0.05$ was considered statistically significant.

Results

We found 24, 22, and 11 of 57 acromegalic patients to have mild, moderate, and severe facial features of acromegaly, respectively. The proportion of mild features was higher in acromegalic women (58.6%) than in acromegalic men (25.0%).

Figure 2 shows typical photographs of men and women with mild, moderate, and severe features of acromegaly. Patients with mild features, relative to patients with moderate or severe features of acromegaly, were older [59.8 ± 13.2 yr (range 40.2–81.4 yr) *vs.* 51.6 ± 13.6 (19.0–73.6 yr), $P = 0.03$] and had lower IGF-I levels [175 ± 81 μg/liter (36–380 μg/liter) *vs.* 370 ± 261 μg/liter (82–1328

FIG. 2. Representative examples of male and female patients with severe (*upper row*), moderate (*middle row*), and mild (*lower row*) facial features of acromegaly.

μg/liter), $P = 0.001$] but no significant differences in spontaneous GH levels [1.7 $\pm$ 0.2 μg/liter (0.2–13.2 μg/liter) *vs.* 5.5. $\pm$13.1 μg/liter (0.2–76.4 μg/liter), $P = 0.22$]. The percentage of biochemically controlled acromegaly was 73.9% in subjects with mild features and 37.5% in subjects with moderate or severe features of acromegaly.

In sex-specific analyses, in women, the correct classification rates of frontal views using different similarity functions ranged from 53.4 to 74.1%, with function P yielding the best result. In men, correct classification rates of frontal views ranged from 67.2 to 84.5%, with function D yielding the best result.

Similar results were achieved if we used the pictures taken with the Ixus camera (Canon) instead of the EOS camera (Canon) in those controls in which pictures with both cameras were taken. Classification results were similar if we excluded 14 patients photographed with the Ixus camera and their respective controls (best correct classification rates 67.4 and 82.6% in women and men, respectively).

Inclusion of side views improved classification for most functions, with function P yielding the best correct classification rate of 81.0% in both men and women. A further improvement of classification was achieved if a combination of a Gabor jet-based and a geometry-based function was used. With this approach, maximal correct classification rates of 81.0 and 86.2% were achieved in women and men, respectively. In women the maximal correct classification rate of 81.0% was achieved with the combination of the functions P+E and in men the maximal correct classification rat of 86.2% was achieved with the combinations of the functions A+L, C+L, P+L, and D+L.

If analyses were not done separately by sex, the maximal correct classification was 80.0%, achieved with the combinations of the functions P+L and P+E. Therefore, and because sex-specific facial features might interfere with the features of acromegaly, we decided to continue with analyses stratified by sex. For final analyses, we chose the combination of functions that yielded the balance of best classification results in both women and men. With the combination of the functions P+L, correct classification rates were 77.6 and 86.2% in women and men, respectively.

Table 1 summarizes the results of classifications with functions P+L and visual ratings by experts and general internists. If the numbers of subjects correctly classified were added, 81.9% of subjects in the whole sample were classified correctly by the software. The classification accuracy among patients and controls was 71.9 and 91.5%, respectively. Patients with mild, moderate, and severe facial features of acromegaly were correctly classified in 58.3, 77.2, and 90.9%, respectively. Among the 16 pa-

TABLE 1. Classification accuracy in percent by software, medical experts in acromegaly, and general internists

Classification	Software[a]	Experts[b]	Internists[c]
Correct classification rates (%)			
Overall	81.9	72.1	64.9
Acromegaly	71.9	63.2	42.1
Controls	91.5	80.8	87.0
By sex			
Acromegalic women	62.1	48.3	26.4
Control women	93.1	82.8	89.7
Acromegalic men	82.1	78.6	53.6
Control men	90.0	76.7	84.4
By severity of facial features in acromegaly			
Mild	58.3	38.9	20.8
Intermediate	77.3	74.2	47.0
Severe	90.9	93.9	78.8

[a] Classification by software, using a combination of the Gabor jet-based function P (normed scalar product including phase) and geometry-based function L (edge difference length) on frontal and side views of patients and controls.

[b] Means of visual classification by three medical experts with extensive experience in acromegaly.

[c] Means of visual classification by three general internists not particularly experienced with acromegaly.

tients with acromegaly who were misclassified by the software, 10, five, and one patient had mild, moderate, and severe features of acromegaly, respectively. Classification accuracy by the software was 80.7% in patients with active acromegaly and 65.5% in patients with controlled acromegaly.

Classification accuracy of patients and controls by experts was 63.2% (range 54.4–75.4%) and 80.8% (range 72.7–93.2%), respectively. This resulted in an overall classification accuracy of 72.1% (range 69.0–76.7%). Classification accuracy of patients and controls by internists was 42.1% (range 33.3–47.4%) and 87.9% (range 84.7–88.1%), respectively, resulting in an overall classification accuracy of 64.9% (range 61.2–67.2%).

Classification accuracy for patients with moderate or severe facial features of acromegaly was similar by software and by experts but lower by general internists. However, the software achieved higher classification accuracy in subjects with mild acromegaly than experts and general internists (58.3 *vs.* 38.9 and 20.8%, respectively). Also, classification accuracy of acromegaly in men was similar by medical experts and software and lower by internists, whereas the software achieved a higher classification accuracy of acromegaly in women than experts and internists (62.1 *vs.* 48.3 and 26.4%, respectively).

Discussion

In this study we tested a novel approach to the detection of acromegaly using software calculating a similarity function between facial images. We found that 72% of acromegalics patients and 92% of controls were correctly classified by the software, whereas the rate of correct visual classification by medical experts was about 10% lower for both patients and controls and clearly lower by general internists.

Thus, our hypothesis that the software outperforms physicians not familiar with acromegaly was proven. Moreover, unexpectedly, the software even outperformed acromegaly experts.

As expected, the accuracy of classification increased with the severity of facial features of acromegaly and was higher in patients with active relative to controlled acromegaly. A higher accuracy was achieved in men than women with acromegaly. This is most likely due to the fact that facial features were milder in women than men. Classification accuracy in acromegalic women by the software was about 15 and 35% higher than by experts and internists, respectively. Additionally, among patients with mild facial features of acromegaly, the classification accuracy of the software was about 20 and 40% higher than by experts and internists, respectively. This indicates that the software performed particularly well among patients with a mild expression of acromegaly that might be easily overlooked by the treating physician.

We are not aware that it has been attempted previously to test classification accuracy of acromegaly by computerized face classification in a database this size and to compare it with recognition rates by medical experts and general practitioners. In a preliminary study, Learned-Miller *et al.* (8) found classification results that were comparable with ours using computer software to detect acromegaly.

However, their study differed from ours in several aspects. First, their study was smaller and they included only 25 acromegalics and 24 controls. Second, pictures of patients and controls were taken at different locations and with different camera specifications. Third, they used a different approach, a morphable model that incorporates camera specifications, thus additionally allowing for systematic error. Fourth, unlike in our study, patients and controls were not matched for age, sex, and ethnicity and patients in their study were of mixed sex and ethnicities, whereas all controls were white men. The last three points represent different potential sources of systematic error that might exaggerate the true difference and thus classification accuracy.

We tried to minimize sources of bias by matching patients and controls by age and sex, by including only Cau-

casian subjects, and by taking pictures of patients and controls under standardized conditions. Moreover, our study was larger, allowing for a better training set and for subgroup analysis by sex or severity.

We are well aware that the setting for visual classification we used differs to the setting of everyday clinical practice. However, the main aim of this setting was to get an impression of visual classification by first sight. One potential source of bias might arise from the fact that the pictures of the first 14 patients were taken with a different camera from the following ones. We addressed this question by comparing classification results in subjects photographed with both cameras and by excluding patients photographed with the first camera and their respective controls. The results were comparable. Therefore, we concluded that bias induced by this fact is likely to be small.

A further limitation of our study is that we do not know whether our results are generalizable to other populations or settings. We intentionally chose a very standardized setting to limit bias. Further studies are needed to test generalizability and to validate our results.

Acromegaly is a chronic disease accompanied by increased morbidity and mortality. Diagnosis of acromegaly is delayed by many years in most patients. It is highly likely that most patients will benefit by an earlier diagnosis since complications can be prevented or addressed at an earlier stage. Moreover, we have previously shown that acromegaly is clearly underdiagnosed in the general population, and many previously undetected cases of acromegaly can be found if they are actively screened for (11). This underscores the need of improved screening strategies for acromegaly.

Our approach by face classification software might help detecting acromegaly in earlier stages. The fact that our software was clearly better than general internists and even better than acromegaly experts in detecting mild cases of acromegaly is very promising. Thus, it might be a helpful tool in detecting subjects with mild acromegaly at an early stage. The system is very simple. It requires only one or two photographs taken with a regular camera. Therefore, it can be used as a screening tool in settings in which blood sampling is not part of routine examinations or specialized laboratory methods are not available. Potential fields of applications include the practices of primary care physicians, dentists, neurologists, endocrinologists, or even Internet-based applications.

However, before general application, several issues need to be addressed. Even though face detection is done by software, in its current state, manual editing is still necessary for optimal results. Future research will aim at improving automatization of this method. Additionally and more importantly, ethical issues need to be considered. This software can be used as a diagnostic tool. Therefore, it should be used with the same precautions as any other diagnostic tool: individuals who are tested should be informed about the meaning and potential consequences of both positive and negative results. Also, it should not be used without consent of participating individuals. Moreover, the diagnosis or suspicion of acromegaly, whether correct or not, may be considered stigmatizing by some people. This always needs consideration when this type of technique is used in the future.

In conclusion, we showed that detection of acromegaly by face recognition works well and even outperforms acromegaly experts. This is particularly the case for patients with mild facial features of the disease. This might be a promising tool to help detection of acromegaly earlier. However, improvement of automatization and validation in further studies is necessary. Moreover, ethical issues, particularly with regard to patients' consent to a diagnostic procedure, should always be kept in mind with the use of this technique.

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