The Marshall and Stickler syndromes: objective rejection of lumping

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SUMMARY To answer the question of whether nosological splitting of the Marshall and Stickler syndromes is justified at the phenotypic level, we surveyed published reports on the two syndromes and applied an objective method to determine this. A set of 18 patients with clinical description, photographs, and radiographs was used to tabulate a list of 53 signs. Cluster analysis using these signs showed that there are two groups of patients with different phenotypes. An index score based on the 20 most discriminating signs was applied to other reported patients and the authors' diagnosis confirmed. There is therefore no objective reason to consider that these two syndromes are not separate dominant disorders with variable expressivity.

The question of whether nosological splitting of the Marshall and Stickler syndromes is justified at the phenotypic level was first raised by Cohen in 1974.¹ He proposed the demise of the Marshall syndrome. Baraitser,² in a more recent publication, suggested that the Marshall and Stickler syndromes are the same autosomal dominant condition with variable expressivity. His opinion was based on a follow-up of a family previously reported as having the Marshall syndrome.³ One subject in the family developed a retinal detachment and was mentally dull. Radiographic anomalies such as platyspondyly and flattening of the epiphyses in the lower limbs were documented in the proband. These findings, which have been described in both the Marshall⁴ and the Stickler⁵ syndromes, were interpreted by Baraitser as evidence for the diagnosis of Stickler syndrome. We have therefore surveyed published reports on the two syndromes and have applied an objective method to determine whether the lumping of the two syndromes is justified.

Materials and methods

PATIENT SELECTION

Previously published reports on either the Marshall or Stickler syndromes were checked for the quality of the photographs of the patients and the completeness of clinical description. Starting with 57

papers, 23 were omitted for absence of photographs and 11 for poor description of the patients. Of the remaining 23 papers, comprising 72 patients, diagnosis of Wagner-Stickler syndrome was proposed in 16 papers, of Marshall syndrome in four and of Pierre-Robin syndrome in three. These 72 patients were used to develop the list of descriptive signs, but only 17 of them were finally entered into the study as being informative enough, by inclusion of a radiographical and ophthalmological report. Another additional unpublished patient from the Montreal Children's Hospital was included (table 1). Additional information on the three patients reported by Popkin and Polomeno¹⁰ was also available from this source. Patients 1 to 3 are from a single family as are patients 5 to 7 and 13 and 14.

SELECTION AND EVALUATION OF SIGNS

All the signs mentioned in the papers or observed by us in the photographs were tabulated. The initial list contained 115 signs, 40 describing the facial dysmorphism, 20 the ophthalmological findings, and 17 the skeletal anomalies. Signs occurring in only one patient were omitted as were those which could not be evaluated in at least 13 patients. Myopia was omitted since all patients had this feature. The 53 remaining signs are listed in table 2. Each sign has two states (normal and abnormal) or more (counter-states or ordered states). The signs were coded independently by the two authors and a consensus was established for any differences in coding.

TABLE 1 Sources of patients used in the study.

Patient		Authors' diagnosis
Number	Source	
1-4	Keith <i>et al</i> ³ (1-4); Baraitser ² (1-3)	Marshall syndrome
5-7	O'Donnell <i>et al</i> ⁶	
8	Herrmann <i>et al</i> ⁷ (patient 5, V.53)	
9	Maunee ⁸	
10-11	Nielsen ⁹	Wagner-Stickler syndrome
12-14	Popkin and Polomeno ¹⁰	
15	Regenbogen and Godel ¹¹	
16	Hall ¹² (patient V.2)	
17	Knobloch ¹³ (patient III.4)	
18	Unpublished	

TABLE 2 Fifty-three characters used to analyse the phenotype of patients (n=normal state).

Sign	State		
	1	2	3
Face			
Shape	Long	n	Round
Asymmetry	Yes	n	
Mala	Flat	n	
Midface	Flat	n	Prominent
Forehead			
Metopic suture	Prominent	n	
Shape	Flat	n	Prominent
High eyebrows	Yes	n	
Eye, external			
Hypertelorism	Yes	n	
Slant	Up	n	Down
Epicanthus	Yes	n	
Strabismus	Yes	n	
Eye, internal			
Astigmatism	Yes	n	
Anterior chamber angle	Abnormal	n	
Iris anomaly	Yes	n	
Cataract	Yes	n	
Retina	n(1)	Degenerate(2)	Detached(3)
Nose			
Root	Flat	n	
Bridge	Prominent	n	Flat
Tip	Broad	n	
Wings	Thick	n	
Columella	Short	n	
Nares	Anteverted	n	
Size	Short	n	Long
Philtrum			
Long	Yes	n	
Prominent	Yes	n	
Mouth			
Arched	Yes	n	
Upper lip	Thick	n	
Lower lip	Everted	n	
Cleft palate	n(1)	Submucous, soft, uvula(2)	Hard(3)
Teeth			
Malocclusion	Yes	n	
Prominent	Yes	n	
Abnormal	Yes	n	
Chin			
Mandible	Small	n	
Retrognathia	Yes	n	
Ears			
Rotation	Posterior	n	
Protrusion	Yes	n	
Sensorineural deafness	Yes	n	
Nervous system			
Mental retardation	Yes	n	

TABLE 2—continued

Size and habitus			
Stature	Tall	n	Short
Build	Thin	n	Stocky
Chest			
Pectus	Yes	n	
Joints (clinical)			
Flexibility	Hyper	n	Hypo
Large	Yes	n	
Genu	Varum	n	Valgum
Talipes varus or valgus	Yes	n	
Talipes planus	Yes	n	
Limbs (x-ray)			
Metaphyses	Wide	n	
Epiphyses	Dysplasia	n	
Bone age	Delayed	n	
Hips, spine (x-ray)			
Iliac wings	Small	n	Wide
Vertebrae	Anomaly	n	
Skull (x-ray)			
Calvarium	Thick	n	
Dura	Calcified	n	

NUMERICAL EVALUATION

The techniques used for the numerical analysis have been previously described¹⁴ and applied.^{15 16} To summarise the techniques, a phenotypic similarity is measured between all pairs of patients independent of the initial diagnosis. Patients are represented as being certain distances from one another based on their phenotypic similarity in multidimensional space. The array of patients can be projected onto a two dimensional surface to visualise the distance between patients.

Results

The results of cluster analysis reflect that there are two groups of patients with different phenotypes (fig 1). Cluster 1 comprises the seven patients described as having the Marshall syndrome. The remaining patient in cluster 1¹³ was thought to have the Wagner-Stickler syndrome (table 1). She is unfortunately the only member of a family of five affected subjects who was usable for this study. The limited clinical data available on the other family members do not allow any conclusions about their diagnosis. All have ophthalmological and skeletal signs compatible with both syndromes.

Of the three families included in the study, all members of each family fall in the same cluster. In cluster 1, the intrafamilial similarity of the six familial cases is greater than that between them and the two non-familial cases, but the difference is not statistically significant (0.768 ± 0.089 and 0.652 ± 0.041 respectively).

All of the patients in cluster 2 were diagnosed as having the Stickler or Wagner syndrome by the authors of the respective papers.

FIG 1 Principal coordinate analysis of 18 patients. The similarity between patients was based on 53 signs. The boundaries of the two groups enclose patients calculated to be in the same cluster.

The frequency of the signs was compared for clusters 1 and 2. Seven signs had a similar frequency in the two clusters (cataract, broad nasal tip, abnormal teeth, small mandible, mental retardation, delayed bone age, and vertebral anomaly). Of the remaining 46 signs, the states had different frequencies in the two clusters. Those whose frequency differed most markedly are presented in table 3. Three equally good discriminators (width of the iliac wings, thick calvarium, and talipes planus) were omitted from the list because they could not be evaluated in all of the patients. Small iliac wings were more frequent in the Marshall cluster and wide iliac wings in the Stickler cluster; a thick calvarium was found only in the Marshall cluster and talipes planus only in the Stickler cluster.

Each state of the signs was given a score according to its relative frequency in the two clusters. In fig 2 we present the distribution of the scores for the 20 most discriminating signs in the 18 patients, to show that the two clusters are completely separated.

Seven patients who were excluded from the study for incomplete clinical data were scored and compared to the distribution in the study group for the sub-set of characters that could be evaluated in each. Four patients were presented as the Marshall syndrome (Marshall⁴: patients 6 and 7; Zellweger *et al*¹⁷: patients 1 and 2) and all had positive scores in the range for the Marshall syndrome. One was presented as the Stickler syndrome¹⁸ and two as a retinopathy and clefting syndrome (Daniel *et al*¹⁹:

FIG 2 The scores for the 18 patients in the study based on the 20 most discriminating signs. The mean and SD of clusters 1 and 2 are $+10.22 \pm 2.88$ and -9.03 ± 2.35 respectively.

TABLE 3 The 20 most discriminating signs between cluster 1 (Marshall syndrome) and cluster 2 (Stickler syndrome).

Sign	State with the highest frequency	
	Cluster 1 (n = 8)	Cluster 2 (n = 10)
Face		
Shape	Round	Normal, long
Asymmetry	No	Yes
Midface	Flat	Normal, prominent
Forehead		
Shape	Prominent	Normal, flat
High eyebrows	Yes	No
Eye		
Astigmatism	No	Yes
Abnormal angle of anterior chamber	No	Yes
Nose		
Flat root	Yes	No
Bridge	Flat	Normal, prominent
Short columella	Yes	No
Anteverted nares	Yes	No
Size	Short	Normal, long
Mouth		
Thick upper lip	Yes	No
Teeth		
Prominent	Yes	No
Chin		
Retrognathia	No	Yes
Size and habitus		
Stature	Short	Normal, tall
Build	Stocky	Normal, thin
Chest		
Pectus	No	Yes
Joints		
Flexibility	Hypo, normal	Hyper
Genu	Varum, normal	Valgum

patient 1; Feiler-Ofry *et al*²⁰) and all had negative scores in the range for the Stickler syndrome. These results support our belief that the two syndromes have a specific pattern of findings even though they share many features.

Discussion

Many of the discriminating signs in this analysis are facial features (table 3). This is probably because they were more carefully and consistently assessed by us from the photographs than was possible for other signs. In the Marshall syndrome, patients have a flat or retracted midface whereas those with the Stickler syndrome have a flat mala which is often erroneously described as a flat midface (Nielsen⁹: cases 1 and 2; Regenbogen and Godel¹¹; Blair *et al*²¹: case 5). The nose differs mainly in the global size, the height of the root, and the length of the columella. The radiological skull findings would also be good discriminants but unfortunately the skull was evaluated in very few patients. All of the Marshall patients who had a skull radiograph had a thick calvarium, abnormal frontal sinuses, and intracranial calcifications. The relative size of the

eyeballs was not included as a sign in our study because of the difficulty in evaluating it in patients of widely differing ages. The impression of large eyeballs in the Marshall syndrome may be the result of midface retraction with relative protrusion of the globe from a shallow orbit.

Many methodological problems are attached to this study. Firstly, we used published case reports, the authors of which are from different disciplines. About a half of the Stickler patients were reported by ophthalmologists and the other half by paediatricians, whereas all of the Marshall patients were described by paediatricians. Secondly, only 17 patients of hundreds mentioned in the literature were included. However, since we chose the cases only on the basis of complete description, photographs, and x-rays, this should not create a bias. A third and probably more serious problem is the small sample size which may not give a good representation of the biological variability of the syndromes. This may have resulted in a wider phenotypic separation of the two groups of patients than is real. However, it seems unlikely that the degree of phenotypic difference apparent in our results could be the result of chance fluctuation. Fourthly, the most discriminating signs in this study differ from those we would have found by a thorough examination of the patients. We therefore do not propose that our list of signs is the best one to classify patients.

Despite these limitations of the study there appears to be no objective reason for lumping together the Marshall and Stickler syndromes. We would suggest a careful reassessment of known families for intrafamilial variability before deciding whether we are dealing with one or two syndromes. We suggest also that case reports in general on rare syndromes should always include a full clinical description and documentation of the findings. A check list for a systematic evaluation of patients is available on request from the authors.

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