Cardio-auditory Syndromes

Cardiac and Genetic Study of 511 Deaf-mute Children*

A. SÁNCHEZ CASCOS, L. SÁNCHEZ-HARGUINDEY, AND P. DE RÁBAGO

From the Cardiac and Genetic Departments, Fundación Jiménez Díaz, Madrid, Spain

In 1957 Jervell and Lange-Nielsen described a Norwegian family, with 4 sibs who all had deaf-mutism, an extraordinarily long Q-T interval, and fainting attacks. Levine and Woodworth described a new case in 1958. Fraser and colleagues (Fraser, Froggatt, and James, 1964a; Fraser, Froggatt, and Murphy, 1964b; Friedmann, Fraser, and Froggatt, 1966) carried out a survey in the U.K. of almost 1500 deaf-mute children, and discovered 9 more cases; with this British study it seemed clear that there was a recessive type of inheritance. Three more cases have been reported from Norway (Jervell, Thingstad, and Endsjö, 1966) and one from the U.S.A. (Lisker and Finkelstein, 1966). No cases were found in a survey of 369 deaf-mute children from Detroit (James, 1967) nor in another of 211 children from Rome (Puletti, Jacobellis, and Borghi, 1967).

On the other hand, several families have been described (Romano, Gemme, and Pongiglione, 1963; Ward, 1964; Barlow, Bosman, and Cochrane, 1964) in which a dominant pattern of inheritance seems to account for a syndrome of a long Q-T interval plus fainting attacks—possibly due to ventricular fibrillation—but without deaf-mutism.

In 1958, Lewis *et al.* reported a family with associated deaf-mutism and congenital heart disease. This family was described again by Koroxenidis *et al.* in 1966, and it seems clear that the mother and 4 of her 8 children had pulmonary stenosis, either valvular, infundibular, or both; 2 of the affected children were deaf-mute, both also having an atrial septal defect, and one of them an obstructive sub-aortic stenosis and mitral incompetence.

Though the association of deaf-mutism and congenital heart disease could be coincidental, in theory a second (Lewis) cardio-auditory syndrome

may exist because of the presence of obstruction in both outflow tracts in one affected sib. It would be interesting to analyse the relation of this syndrome to the obscure group of obstructive cardiomyopathies.

There are several interesting points to be investigated in relation to the cardio-auditory syndrome (or syndromes). (a) Its prevalence in Southern Europe, i.e. a Mediterranean country, because the gene has been considered to be Nordic in origin (Fraser *et al.*, 1964b). (b) The relation between this syndrome and the Romano-Ward syndrome. (c) The mechanism of inheritance and other genetic analysis. (d) The possibility of detection of heterozygotes by electrocardiogram, as suggested by Fraser. (e) A complete cardiac examination of affected children. (f) A metabolic analysis of affected children.

For these reasons it was decided to carry out a cardiac and genetic survey in 3 deaf-mute schools in Madrid, representing all regions of Spain.

SUBJECTS AND METHODS

Studies were made on 511 deaf-mute children (270 boys, 241 girls). Only those accidentally absent from school were not included in the survey.

The first survey consisted of an auscultatory and electrocardiographic study of all the children. In all, 28 were selected according to the following criteria: (i) a Q-T interval which was long or in the upper normal range; (ii) fainting attacks; (iii) murmurs or arrhythmias.

These 28 children, as well as 15 relatives (parents and sibs) of 7 of them, were subjected to a cardiac and genetic study, consisting of (a) pedigree; (b) dermatoglyphs, i.e. frequency of basic finger patterns (arch, ulnar, or radial loop, whorl), total finger ridge count, and the position of the axial triradius (r) defined by atd angle amplitude, were considered (r° for an angle not wider than 45° ; r' for a wider angle); (c) karyotype; (d) electrocardiogram; (e) cardiac examination; (f) haematological analysis, i.e. erythrocyte count, blood ions, enzymes, and blood groups.

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FIG. 1.—Electrocardiogram at 25 mm./sec. in the proband with the Jervell and Lange-Nielsen syndrome.

RESULTS

(1) *Jervell and Lange-Nielsen Syndrome.* Only one case was found with this syndrome. The proband is the sole surviving child of a third degree consanguineous marriage. Both parents come from Zamora province, an inland part of the northern Spanish plateau. The couple had a previous child, a boy, who clearly had the same syndrome, as he was deaf-mute and frequently fainted; he died during one of these fits.

The proband was born in April 1961, when the parents were 32 and 25 years. There was nothing unusual about

the pregnancy or the delivery, but shortly after birth the child was noticed to be deaf. She has had about 15 fainting attacks, some of them lasting 2–3 minutes, but during none of them was she examined by a doctor or a nurse, though parents and the nuns of the school described her as becoming pallid and falling down, sometimes appearing to be dead: these spells are now shorter and less severe than they were earlier.

These 2 sibs are the sole examples for both syncope and deaf-mutism in the family.

Clinical cardiac examination. The electrocardiogram (Fig. 1) showed enlargement of the Q-T interval, with bizarre pathological T waves. X-rays (Fig. 2) showed

FIG. 2.—X-rays (frontal and left anterior oblique positions) in the proband with Jervell and Lange-Nielsen syndrome.

TABLE I
CARDIAC DATA IN 12 CASES

Case No.	Age (yr.)	Electrocardiogram							X-rays	
		Q-T	R-R	AQRS	V1 pattern	R/S	V6	Others	Left ventricular hypertrophy	Others
1	10	32	60	55°	RS	1.2	qR	Nodal rhythm	++	Right ventric. hypertrophy
2	6	34	64	40°	RS	1.2	qR		++	
3	5	32	64	30°	Rs	1.3	qRs		++	Right ventric. hypertrophy
4	5	34	70	45°	rS	0.6	qR		++	
5	8	36	70	70°	RS	0.8	qRs	T-V1-3 T-V1-3	++	
6	10	32	55	85°	Rs	2	qR		++	
7	12	32	60	0°	RSr'	1.7	Rs		++	
8	10	34	68	90°	RS	0.8	qR	Flat T in V5-6	++	
9	12	30	50	0°	rS	0.5	qR		++	
10	22	33	76	60°	RS	0.8	qR		—	
11	10	29	46	20°	RS	0.9	qRs		—	Ascending aortic dilatation Right ventric. hypertrophy
12	9	32	60	50°	rS	0.7	qRs		+	

cardiomegaly, mainly due to a left ventricular hypertrophy. The father was normal on examination, as was his electrocardiogram. X-ray examination showed left ventricular hypertrophy. Blood pressure was normal.

Clinical, radiological, and electrocardiographic examination of the mother showed nothing abnormal.

The proband and both parents had normal erythrocyte counts, blood ions, transaminases, and lactic dehydrogenase. Blood group was O Rh positive for the proband and mother, and A Rh positive for the father.

Dermatoglyphs. The proband has 8 arches and 2 low count ulnar loops on her finger-tips; there are ulnar loops on both little fingers. The total finger-ridge count is 4. Both palms have t° triradius.

Her father has 4 arches, 5 ulnar loops, and 1 radial loop, with a total finger ridge count of 25. Her mother has 3 arches, 6 ulnar loops, and 1 radial loop, with a finger ridge count of 51. Both parents have t° triradius.

(2) *Congenital Heart Disease.* Two children, a boy and a girl, both selected because of murmurs, were found to have ostium secundum atrial septal defect.

(3) *Arrhythmias.* A boy presented with occasional sinus bradycardia with nodal escapes; he did not faint.

(4) *Possible New Cardio-auditory Syndrome.* When analysing the data, we noticed that x-ray examination showed cardiomegaly in a number of children who also had abnormal electrocardiograms, suggesting biventricular or only right ventricular hypertrophy. Twelve such patients were listed, 4 of whom were ascertained because of faints, and the rest because of a tendency towards high range Q-T values. The x-rays in Cases 1-4 indicated abnormalities, and those of Cases 5-12 were also abnormal.

Cardiac examination (Table I) revealed that the Q-T interval, always within normal limits, used to be in the higher normal range (Fig. 3).

AQRS: half the cases presented a slight left axis deviation.

V1 lead (Fig. 4 and 5) was pathological, with predominant R waves, so that R/S index was higher

FIG. 3.—In this graph the Q-T interval has been plotted against R-R interval. The range values have been calculated according to the Heglin-Holzmanna formula ($0.39 \sqrt{R-R} \pm 0.04$). ● = Proband with Jervell and Lange-Nielsen syndrome (the higher value) and her parents. Δ = Cases with the cardio-auditory syndrome. x = Case with arrhythmia, both cases with atrial septal defect, and the brother of one of these.

FIG. 4.—Electrocardiograms of Cases 1-4.

than 1 in 5 cases. V5-6 showed predominant R waves, so that, as a whole, the electrocardiogram could be interpreted as indicating hypertrophy of both ventricles.

Ten cases had left ventricular hypertrophy on x-ray, which was significant in Cases 1-4 and mild in the other 6. Three cases also presented with an associated right ventricular hypertrophy. There were no other significant cardiac abnormalities.

Genetic data are set out in Table II. There was only one girl among these cases, and she was the

only one with a normal heart silhouette. Only in one case did consanguinity exist. Blood groups, parental ages, and birth order were unremarkable. In three families there were 6 deaf and 4 normal children (6/4). In six more, this relation was 6/23.

Blood counts. The erythrocyte count was between 3.5 and 4.6 million.

Blood ions were normal in every case. Serum enzymes gave normal transaminases and lactic dehydrogenase values.

TABLE II
GENETIC DATA IN 12 CASES

Case No.	Sex	Blood Group	Mother's age (yr.)	Birth order	Sibs		Abortion	Stillbirths
					Deaf	Normal		
1	M	A—	32	3	0	2	—	—
2*	M		45	4	1	2	—	—
3	M		36	8	0	1	2	4
4†	M							
5	M	A—	26	4	0	1	—	2
6	M	O+	36	8	1	2	4	—
7	M	A+	42	15	0	14	—	—
8	M	A+	29	2	0	1	—	1
9	M	O+	29	1	0	2	—	—
10	F	O+	23		1	0	—	—
11†	M	O+						
12†	M	O+						

* First-degree consanguinity.
† Incomplete data, as parents were unwilling to co-operate.

FIG. 5.—Electrocardiograms of Cases 5–12.

Dermatoglyphs (Table III). All patients had a tendency towards a high number of whorls in the fingers (52%, normal is about 25–30%). This resulted in an increase of the total finger ridge count (mean 158, whereas a normal mean value is 145 in men and 127 in women—Holt, 1961). Axial tri-radius occupied a τ° position in all but one case.

DISCUSSION

Including the proven case of Jervell and Lange-Nielsen syndrome, together with her brother who seemed to have the same syndrome, a minimum of 20 cases, from 13 families, have been documented. The family in our study is the only one to have been found in Southern Europe, though a possible

TABLE III
DERMATOGLYPHIC DATA IN 12 CASES

Case No.	Arch	Ulnar loop	Radial loop	Whorl	Total finger ridge count	<i>t</i> position	
						<i>t</i> ^o	<i>t</i> [']
1	—	7	—	3	180	<i>t</i> ^o	<i>t</i> [']
2	—	—	—	10	172	<i>t</i> ^o	
3	—	4	—	6	214	<i>t</i> ^o	
4	—	8	—	2	137	<i>t</i> ^o	
5	2	3	—	5	144	<i>t</i> ^o	
6	1	8	1	—	95	<i>t</i> ^o	
7	1	7	—	2	105	<i>t</i> ^o	
8	—	3	—	7	171	<i>t</i> ^o	
9	—	4	—	6	177	<i>t</i> ^o	
10	—	7	—	3	159	<i>t</i> ^o	
11	—	—	—	10	174	<i>t</i> ^o	
12	—	2	—	8	167	<i>t</i> ^o	
Total	3%	44%	1%	52%	158 (average)	92%	8%

patient, now dead, was found in Italy (Puletti *et al.*, 1967). Four families have been reported from Norway (Jervell and Lange-Nielsen, 1957; Jervell *et al.*, 1966), six from the U.K. (Fraser *et al.*, 1964a, b), and two from the United States (Levine and Woodworth, 1958; Lisker and Finkelstein, 1966), the first of these with Finnish ancestry, according to Fraser. Fraser and colleagues found a geographically unequal distribution in the U.K., finding more cases in Ulster and in the northern part of East Anglia, places where Viking and Anglo-Saxon races predominate, and they considered the probability of a Nordic origin for the gene. Finding a case in the centre of Spain, a region in which the possibility of Nordic genes can be ruled out, certainly does not exclude a high Nordic gradient for this gene; but it is worth reporting its existence in Mediterranean races.

It is difficult to calculate the real frequency of a recessive gene when homozygotes are known to have a detrimental condition. We found 1 child among 511 deaf-mute children attending three schools for deaf-mutes in Madrid; on the other hand, the proband's brother would have been attending the school had he not died; and other affected children do not perhaps attend schools because of their fainting spells. There are in Spain more than 30,000 deaf-mutes, but we do not know how many of the theoretically affected ones have died. Fraser has calculated that the approximate prevalence of the syndrome in Britain could be 3 per million total births (Fraser *et al.*, 1964a).

Three in the 12 previously reported families and also the one of this study presented familial aggregation; in them, all affected members were sibs. In so far as at least 4 families, including ours, had parental consanguinity, a recessive pattern of inheritance seems clear. Both sexes are represented

—8 males and 12 females among 20 cases (a 2:3 ratio, deviation from expected 1:1 being perhaps due to a higher mortality for the male carriers).

To the best of our knowledge this case is the first in which there was dermatoglyphic analysis. The proband as well as both her parents have an unusually high number of arches on their fingers; consequently the total finger ridge count is very low for all of them, since arches count as 0. The proband has 8 arches, but even the two other fingers, both little fingers with ulnar loops, have a very low ridge count, so that total finger ridge count scores 4; this figure is typical for 18-trisomy, but families exist with a very low total finger ridge count due to the exclusive or dominant presence of arches, and we have seen a number of such families without any kind of anomaly. In this particular family the high number of arches could be related to the cardio-auditory syndrome, but obviously more families would have to be analysed before this dermatoglyphic pattern could be considered a feature of the Jervell and Lange-Nielsen syndrome. Should that hypothesis prove correct, the trait would be useful for heterozygote detection.

The value of a slight prolongation of the Q-T interval in detection of heterozygotes has been indicated by Fraser *et al.* (1964a) and Jervell *et al.* (1966), but it is not easy to define the upper range of values for the Q-T interval with confidence. Both parents in our case had a normal Q-T interval, according to the Hegglin and Holzmann formula (Fig. 3).

We think our case is the first in which left ventricular hypertrophy existed, and the father also had left ventricular hypertrophy; but neither he nor the proband had any valve lesion or systemic hypertension to account for it.

The cause of fainting and the reasons for the

prolongation of the Q-T interval have been exhaustively discussed previously: no definite explanation has been found, but a metabolic cause seems to be ruled out. We have nothing to add to this as our family's data were normal. Fraser *et al.* (1964a) were able to find some histological lesion in the Purkinje system that could account for Q-T prolongation and even for an arrhythmic nature of syncope and sudden death; but whether this finding is primary or whether it depends on anoxia during spells is difficult to decide.

The presence of left ventricular hypertrophy in the proband as well as in her father suggested to us that the Jervell and Lange-Nielsen syndrome could be a special type of cardiomyopathy. Sudden death and faints caused by fright, anger, or fear possibly relate this syndrome to some adrenergic mechanism; an excess of cardiac catecholamines is nowadays thought to account for outflow obstruction and cardiomegaly in cardiomyopathy (Goodwin, 1967).

In this connexion, it is interesting to consider the family reported first by Lewis *et al.* (1958) and Koroxenidis *et al.* (1966). Association of congenital heart disease with deaf-mutism in its members could be coincidental, but the possibility exists that it represents a second (Lewis) cardio-auditory syndrome, related again to cardiomyopathies, since one affected member presented subaortic obstruction plus infundibular stenosis as well as atrial septal defect. Our series presented two cases of atrial septal defect; whether they represent an example of this second (Lewis) cardio-auditory syndrome is difficult to assert, as the presence of two cases of atrial septal defect among 500 random children could be coincidental.

One case in our series presented an arrhythmia without fainting. Its presence is reputed also to be coincidental.

Finally, in the analysis of the cardiac data from our deaf-mute series, several cases emerge that could represent a new (3rd) cardio-auditory syndrome. It seems to be defined by a radiological left ventricular hypertrophy (on some occasions it was associated with a right ventricular hypertrophy), plus an electrocardiogram with a tendency to a high R in V1 (R/S quotient in that lead is always high for a child's age) and also a high R in V5-6, together with a tendency in some cases towards left axis deviation (these electrocardiograms being typical of Duchenne's muscular dystrophy—Perloff *et al.*, 1967); the Q-T interval is within the range of normal values, but some cases show a tendency towards higher than normal values.

Four cases clearly belonged to this syndrome and 8 more probably belonged. The cardiomegaly of

this syndrome seems once more to represent a link between cardio-auditory syndromes and cardiomyopathies. Dermatoglyphic analysis of these 12 cases seems to present a pattern, with a high incidence of whorls (52%, while the incidence in controls is about 25–30%), and consequently a high total finger ridge count. There was only one girl in these 12 children, and she was not a definite case; the possibility of a sex-linked gene therefore exists.

SUMMARY

The authors carried out a cardio-genetic study of 511 deaf-mute children. One girl had the Jervell and Lange-Nielsen syndrome. Her parents were consanguineous and an elder sib, a boy, who had died previously, also had the syndrome. The family was interesting from a dermatoglyphic point of view: the proband had 8 arches and 2 ulnar loops, with total finger ridge counts scoring 4; both parents also had a high number of arches on their fingers.

Twelve more children were found to present some common features that could define a new cardio-auditory syndrome: all but two had radiological evidence of left ventricular hypertrophy; most of them had a high R/S quotient in V1, with a suggestion of biventricular hypertrophy; in some cases there was a tendency towards left axis deviation. In most cases, dermatoglyphs showed an increase in the total finger ridge count due to the high number of whorls.

The relation between these cardio-auditory syndromes and cardiomyopathies is discussed.

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