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ARTICLE

A New Phenotypical Variant of Intrauterine Growth Restriction?

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ABSTRACT

OBJECTIVES. A link between intrauterine growth restriction and major adult-onset diseases has been reported. In this study we observed a series of hitherto-unrecognized clinical features in a population of children with intrauterine growth restriction.

PATIENTS AND METHODS. A total of 77 Italian children (aged 9.45 ± 2.08 years) with antenatally diagnosed intrauterine growth restriction and small-for-gestational-age birth, along with their parents, were examined. The children with intrauterine growth restriction and were small for gestational age were subdivided into 2 groups ("variant" versus control subjects) according to evidence of auricle morphology deviation from normal. The following variables were determined: (1) external ear auricle geometry; (2) function of the posterior communicating arteries of the circle of Willis, as assessed by transcranial Doppler ultrasonography; (3) articular mobility, as assessed by Beighton's 9-point scale; (4) skin softness; and (5) distortion product–evoked otoacoustic emissions.

RESULTS. Intrauterine growth restriction–variant children (n = 27) showed a significant female predominance, a lower proportion of maternal pregnancy-induced hypertension/ preeclampsia, and a higher head circumference as compared with intrauterine growth restriction control subjects. Mothers of small-for-gestational-age–variant children showed significantly different auricular geometry parameters as compared with the intrauterine growth restriction controls mothers. An excess of bilaterally nonfunctioning posterior communicating arteries was observed both in the children with the intrauterine growth restriction–variant phenotype and their mothers as compared with the control groups. Significantly increased proportions of joint hypermobility and skin softness were observed in the intrauterine growth restriction–variant children as compared with controls subjects. Children

with the intrauterine growth restriction–variant phenotype and their mothers showed bilateral distortion product–evoked otoacoustic emissions notches versus none in the control subjects, with an associated reduction of the area under the curve in both the intrauterine growth restriction–variant children and their mothers. No significant differences between the variant and control groups regarding the fathers were observed.

CONCLUSIONS. We propose that the observed phenotypical constellation may represent an unrecognized variant of intrauterine growth restriction.

INTRAUTERINE GROWTH RESTRICTION (IUGR) has a prevalence of 10% among all pregnancies, varying from rates of 3% to 5% among healthy mothers up to ≥25% in high-risk groups.[1] IUGR resulting in birth weight small for gestational age (SGA) is a known risk factor for high perinatal morbidity and mortality and has been related previously to development of several of the major diseases of later life, including coronary heart disease, obesity, noninsulin dependent diabetes, hypertension, and stroke.[2,3] Studies linking IUGR with long-term adverse health consequences have so far depended on crude measures of fetal growth, such as overall weight or length. Recently, fetal growth of liver and kidneys has been shown to be impaired in intrauterine growth-retarded infants, thus supporting the concept that fetal environmentally caused "programming" may increase the risk of functional defects and diseases in later life.[4] However, no morphologic markers of impaired fetal growth that persist later in life are known to date, with the possible exceptions of fingerprints pattern abnormalities and shape of the palm[5] or a high second-to-fourth-digit finger-length ratio[6,7] in specific SGA subsets. Here, we describe a series of children with idiopathic IUGR/SGA showing previously unrecognized, phenotypical features, including auricle shape variations, bilaterally reduced or absent hemodynamic responses of the posterior communicating arteries (PCoAs) of the circle of Willis, joint hypermobility, soft skin, and bilateral subclinical cochlear dysfunction.

METHODS

Subjects

A total of 77 Italian children (boys: 32; girls: 45; gestational age at birth: 35.49 ± 2.50 weeks; age at examination: 9.45 ± 2.08 years) with antenatally diagnosed IUGR (as defined as insufficient fetal growth <2 SD [or <3rd percentile] below the mean for gestational age) and SGA birth (as defined as insufficient body size <2 SD [or <3rd percentile] below the mean for weight and/or length in relation to gestational age and gender for the Italian population),[4,8] followed up in a regular clinical program, were enrolled, along with their parents (mothers, age at examination: 40.57 ± 4.61 years, range: 35–48 years; fathers, age at examination: 42.5 ± 0.71 years, range: 37–49 years). The examined families originated from Tuscany (67 of 77 [87%]), Apulia (8 of 77 [10.4%]), and Basilicata and Sicily (1 of 77 [1.3%] each). The percentiles for body height and weight at examination were determined on the basis of Italian cross-sectional growth charts.[9] None of the participants had primary growth failure syndromes, congenital infections, known chromosomal aberrations, genetic syndromes, or showed specific dysmorphic features or developmental delay. None of the participants had a history of cerebrovascular disorders or preexisting systemic illness, known cochlear disease, history of environmental noise exposure, or inherited connective tissue diseases. After providing their respective histories, all of the subjects underwent a complete physical examination. Low maternal weight was defined as prepregnancy or delivery weight <45.36 kg or BMI ≥19.8 kg/m², and low maternal weight gain was defined as <0.27 kg per week.[10] None of the mothers had a history of malnutrition and/or chronic use of alcohol or narcotics. None of the examined parents had a history of past or current smoking, hypertension, hypercholesterolemia, or diabetes mellitus. The IUGR/SGA children were subdivided into 2 groups (variant versus control subjects) according to subjective evidence of auricle morphology deviation from normal (Fig 1A), and the following variables were determined: (1) external ear auricle geometry; (2) PCoA function, as assessed by transcranial Doppler ultrasonography; (3) articular mobility; (4) skin softness; and (5) distortion product–evoked otoacoustic emissions (DPOAEs). The main reason for doing a long-term clinical follow-up in our IUGR/SGA children was an arterial pressure monitoring study.[11,12]

The follow-up was systematic, without previous sample selection. Our follow-up "theoretical" duration is up to age 14 years. Approval from the institutional review board and informed consent for clinical examination, instrumental studies, and photographic imaging were obtained.

External Ear Geometry

The maximum width of longest axis (LA), shortest axis (SA) of the auricle, and the distance of SA from the lowest auricle point (SA-D) were measured (Fig 1A). SA/LA and LA/SA-D ratios were used as size-independent geometric indicators of auricle shape. The SA-D and SA/LA ratios from both ears were evaluated, and the mean of the measurements was used for each individual in the analyses. Morphometric measurements of the auricle were collected with Vernier calipers to 0.01-mm accuracy by 2 operators who were unaware of the results of the other clinical and/or instrumental findings. The asymmetry index was also calculated by subtracting the average length of the right side of the trait from the
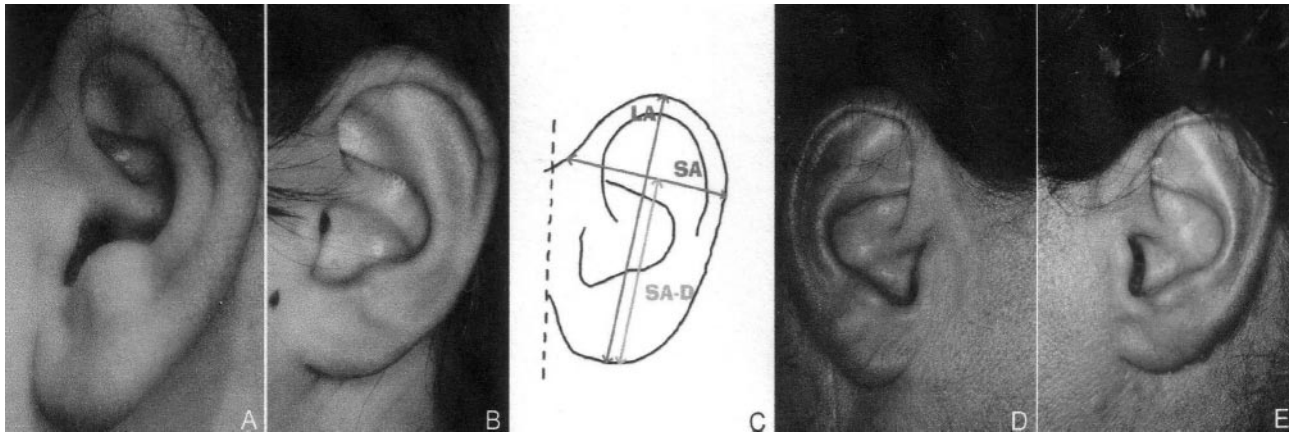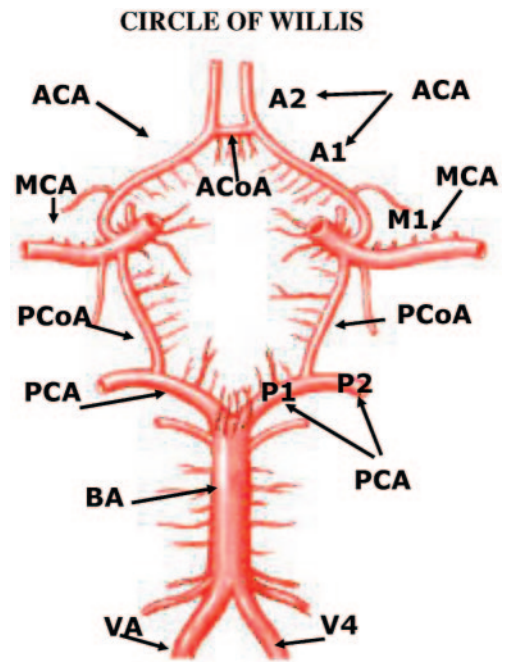
FIGURE 1
Auricle shape in the IUGR/SGA variant and their mothers. A, Variant; B, IUGR/SGA control child; C, schematic graph; D and E, ear shape: right-to-left asymmetry in the mother of a child with the IUGR/SGA variant.

left and correcting for trait size (ie, $100 \times$ right $-$ left/[right $+$ left]/2).[13]

Transcranial Color-Coded Duplex Ultrasonography
Ultrasound flow-flow examination was performed with a color-duplex scanner (Philips Sonos 5500, Agilent Technologies, Hewlett-Packard, Andover, MA), using either a 3- to 11-MHz linear transducer or a 2.5-MHz 90° sector transducer head for evaluating the extracranial carotid and vertebral arteries and the intracranial basal arteries, respectively. Examination of the internal carotid (intracranial tract), vertebral artery (V4 segment), and basilar artery, as well as in the anterior (precommunicating, A1 segment), middle (main trunk, M1 segment), and posterior (precommunicating and postcommunicating, P1-P2 segments) cerebral arteries through the temporal bone window, was performed according to standard techniques[14–16] (see Fig 2 for a diagram with the segments of the circle of Willis). All of the subjects showed sufficient acoustic windows. The blood flow velocity changes in the precommunicating parts (A1 and P1, respectively) of the anterior and posterior cerebral arteries were measured during common carotid artery (CCA) compression. To avoid a systemic cardiovascular reaction, compressions were applied for 3 to 5 cardiac cycles, low in the neck just proximal to the sternal head of the clavicle. The anterior communicating artery was defined as functional if blood flow was reversed in the ipsilateral A1 and enhanced in the contralateral A1 during CCA compression. The PCoA was considered to be functional if the flow velocity in the P1 was enhanced >20% during ipsilateral CCA compression. PCA was defined as fetal configuration (ie, the major stem of the PCA arising from the ipsilateral internal carotid artery instead of from the basilar artery) in case of significant decrease in peak velocity after CCA ipsilateral compression. The transcranial color-coded duplex ultrasonography was conducted by a single operator blind to further

FIGURE 2
Schematic diagram of the arterial segments of the circle of Willis as identified by transcranial color-coded duplex ultrasonography.

clinical or instrumental information. The methodology used was standard and sufficiently reproducible (κ = 0.93 [SE: 0.021]; range: 0.89–1.0).

Joint Hypermobility
Joint hypermobility was evaluated using the Beighton's 9-point scale[17] by clinicians blind to other clinical or instrumental information. In children, joint hypermobility was defined as the presence of ≥ 3 of 5 positive criteria, according to Beighton and Carter,[17,18] and in their parents as a mobility score >4.[19]

Skin Softness

An excessive skin softness was evaluated as a subjective variable by 2 independent observers (interobserver agreement for increased skin softness: $\kappa = 0.910$ [SE: 0.025]; range: 0.846–1.0) who were unaware of the subjects' clinical history and findings.

Distortion Product–Evoked Otoacoustic Emissions

Otoacoustic emissions, expressing the response that the cochlea emits in the form of acoustic energy, are determined by the contractile activity of the outer hair cells and the mechanical and structural features of the basilar membrane. Otoacoustic emissions are currently used as objective indicators of cochlear pathology and used in several neonatal hearing loss screening programs.[20,21] In the present study, cochlear function (DPOAEs) was investigated in all of the IUGR/SGA children and their parents using an ILO 292 DP Echoport OAE Analyzer 5.0 (Otodynamics Ltd, London, United Kingdom).[22–24]

Two simultaneous pure tones were sent to each ear (f2>f1 with an f2/f1 ratio = 1.22, sounds intensity = 70 dB sound pressure level, with a frequency range of 1–6 kHz). The degree of cochlear dysfunction was determined by calculating the area under the curve (AUC) for all of the DPOAE recordings. In case of a detectable "notch" (ie, a marked reduction in the intensity of otoacoustic emissions in the frequency response; Fig 3), its mean peak frequency was determined. All of the subjects had normal otoscopic findings and normal hearing, as preliminarily assessed using pure tone audiometry, tympanometry, stapedius reflex tests, and auditory brainstem responses.

Data Analysis

Differences in categorical and continuous variables between the 2 SGA groups were assessed using χ^2 or Fisher's exact tests and Student's paired t test (Bonferroni corrected significance levels) or Wilcoxon's test, as appropriate. AUC for DPOAEs was determined using a serial measurements algorithm. The MedCalc 8.1.1 statistical software (MedCalc Software, Mariakerke, Belgium) was used. A 2-sided P value of < .05 was considered statistically significant.

RESULTS

A multiple comparison between children with the IUGR variant and controls is shown in the Table 1. The children belonging to the IUGR-variant group showed a significant female predominance ($P = .0226$), a lower proportion of maternal pregnancy-induced hypertension/preeclampsia ($P < .0001$), and a higher head circumference ($P < .0001$), whereas no statistically significant differences were present regarding age at examination, gestational age at birth, history of maternal SGA, percentiles for height and weight at examination, birth weight, and birth length ($P \geq .4991$).

The children with the IUGR variant showed a different auricular geometry, as compared with IUGR control subjects, exhibiting significantly lower SA-D/LA ratios and higher SA/LA and SA-D asymmetry indices (all $P < .0001$; Table 1). Likewise, their mothers showed significantly different auricular geometry parameters as compared with the mothers of IUGR control subjects (SA-D/LA ratio: 0.6247 ± 0.063 vs 0.7049 ± 0.0197, $P =$
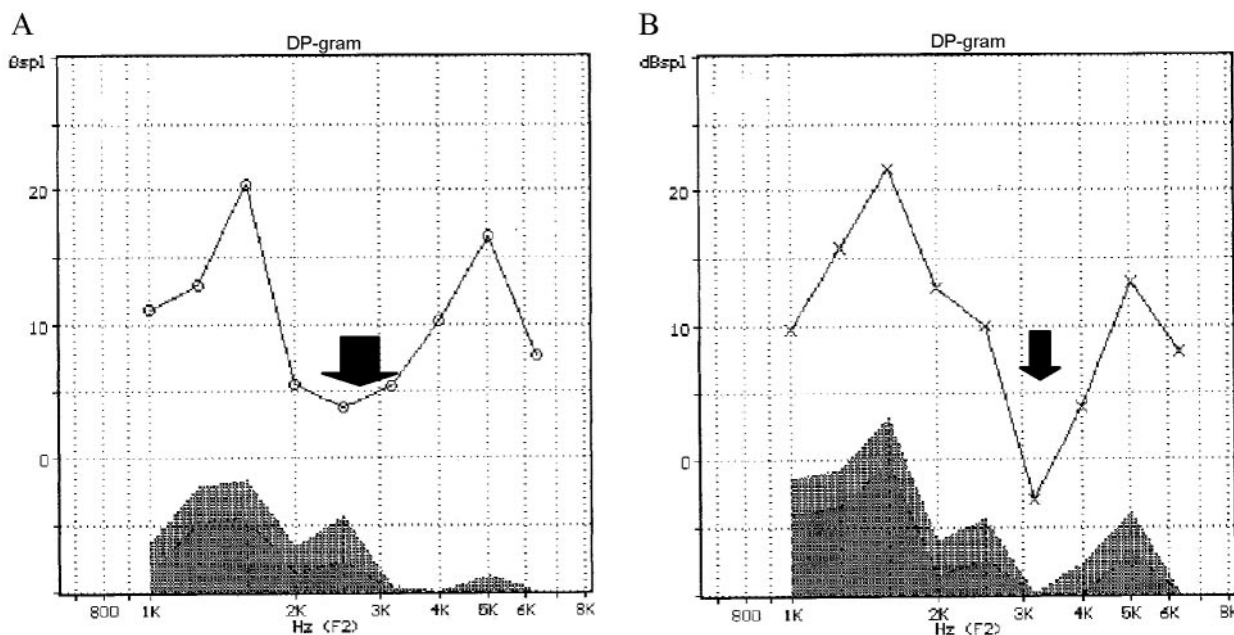
FIGURE 3

DPOAEs in a child with the IUGR/SGA variant (A) and the corresponding mother (B). A notch (ie, a marked reduction in the frequency response) is evidenced (arrows) in both graphs, with a mean frequency peak at ~2.5 kHz in the child and ~3.2 kHz in the mother. The right-ear graph is shown for both subjects. (y-axis: sound intensity, dB SPL; x-axis: sound frequency, kHz).

TABLE 1 Comparisons of Relevant Clinical Characteristics in IUGR/SGA Children With and Without Auricle Shape Variations

Variables	SGA Children	
	Variant Auricle Shape (N = 27)[a]	Normal Auricle Shape (N = 50)
Demographics and pregnancy		
Male/female (% female)	6/21 (77.77)	26/24 (48.0)[b]
Age at examination, mean ± SD, y	9.4 ± 1.65	9.5 ± 1.25
Pregnancy-induced hypertension/preeclampsia, n (%)	2 (7.4)	41 (82.0)[c]
Gestational age at birth, mean ± SD, wk	35.05 ± 5.13	35.09 ± 3.51
SGA mother, n (%)	1 (3.7)	4 (8)
Family history of SGA, n (%)	1 (3.7)	6 (12)
Auxometry, mean ± SD		
Birth weight, g	1484 ± 520	1511 ± 555
Birth length, cm	41.0 ± 3.32	41.4 ± 4.16
Birth head circumference, cm	31.83 ± 1.18	30.0 ± 1.32[c]
Height at examination, percentile[d]	36.14 ± 27.56	41.14 ± 32.42
Weight at examination, percentile[d]	44.43 ± 35.60	38.86 ± 34.42
External ear geometry, mean ± SD		
SA-D/LA ratio	0.5111 ± 0.0066	0.7270 ± 0.0561[c]
SA/LA asymmetry index, %[e]	3.25 ± 0.25	1.50 ± 0.25[c]
SA-D asymmetry index, %[e]	17.99 ± 3.5	3.96 ± 0.21[c]
Transcranial color-coded duplex ultrasonography		
Bilaterally nonfunctional PCoAs, n (%)[f]	27 (100)	0 (0)[c]
Joint hypermobility, n (%)[g]	27 (100)	1 (2)[c]
Beighton's score[h]	5 ± 0.5	2 ± 1.5[c]
Skin softness, n (%)	27 (100)	0 (0)[c]
DPOAEs		
Bilateral notch, n (%)[i]	27 (100)	0 (0)[c]
AUC, right ear, mean ± SD, dB SPL	35.95 ± 14.07	59.55 ± 22.25[c]
AUC, left ear, mean ± SD, dB SPL	23.90 ± 2.69	69.07 ± 14.99[c]

[a] See Fig 1A.

[b] .05 < P ≤ .01.

[c] P < .001.

[d] Data shown are the percentiles at examination, adjusted for age and gender.

[e] Asymmetry index indicates (100 × right − left/[right + left]/2).

[f] Postcompression systolic velocity increase <20% over baseline values in the ipsilateral PCA.

[g] Data include the presence of ≥3 of 5 positive criteria, according to Beighton et al[17] and Carter and Wilkinson.[18]

[h] Values are median ± semi–interquartile range.

[i] A notch is defined as a sharp decrease in the intensity of otoacoustic emissions at middle-high frequencies.

.0040; SA/LA asymmetry index[4]: 12.70 ± 7.52% vs 1.47 ± 0.25%, P = .0009; SA-D asymmetry index: 13.45 ± 3.09% vs 3.96 ± 0.21%, P < .0001) with the exception of the SA/LA ratio (0.5852 ± 0.0546 vs 0.5736 ± 0.016). Ear shape variation was found to be bilateral in the variant IUGR/SGA subjects, whereas it was unilateral in the unaffected variant SGA mothers. By contrast, no significant differences between the variant and control groups were observed regarding the fathers (P ≥ .45; data not shown).

Nonfunctional PCoAs showed postcompression values in the ipsilateral PCA (mean ± SD) of a 4.34% ± 5.98% increase over basal values (range: 0%–11.27%) vs functional PCoAs with a 76.96% ± 26.89% increase over baseline (range: 23.12%–119.06%). A statistically significant excess of bilaterally nonfunctioning PCoAs was observed both in the children with the IUGR variant (P < .0001) and their mothers (26 of 27 [96.3%] vs 0 of 50 [0%]; P < .0001) as compared with the control groups (Table 1). No significant differences were evi-

denced regarding the fathers (P ≥ .8200; data not shown).

Significantly increased proportions of joint hypermobility and skin softness were observed in the IUGR-variant children as compared with control subjects (P < .0001; Table 1). On the other hand, no significant differences were observed concerning articular mobility and skin examination for the parental groups (P ≥ .6515; data not shown), and none of the examined SGA-variant children showed abnormal skin laxity.

All of the children with the IUGR variant and their mothers showed evidence of bilateral DPOAEs notches (Fig 2) as compared with none of the control subjects (P < .0001), with an associated reduction of the AUC in both the IUGR-variant children (P < .0001; see Table 1) and their mothers (AUC right ear: 19.05 ± 18.86 dB of sound pressure level, SPL, vs 48.17 ± 13.41 dB SPL, P < .0001; AUC left ear: 15.11 ± 13.53 dB SPL vs 58.12 ± 18.77 dB SPL, P < .0001). However, the peak frequency of the notches for the variant IUGR children was signif-

icantly lower than that of their mothers (2.63 ± 0.39 kHz vs 3.21 ± 0.27 kHz, $P < .0001$). No significant DPOAE differences were evidenced regarding the fathers ($P \geq .6611$; data not shown). Likelihoods of random association for the described features in individual children and child-mother pairs were estimated to be ~2.25 × 10^{-8}, and ~1.35 × 10^{-9}, respectively.

DISCUSSION

Our findings suggest the presence of a previously unrecognized phenotype in a subset of IUGR/SGA children, based on the following: (1) abnormal auricle shape, related to a minor developmental defect of the helix; (2) bilaterally low hemodynamic responses of the PCoAs; (3) bilateral subclinical cochlear dysfunction; (4) excessively soft skin; and (5) joint hypermobility. In addition, the described IUGR/SGA variant was found to be associated with distinct maternal phenotypic features, including auricle shape changes, transcranial color-coded duplex ultrasonography evidence of bilaterally nonfunctional PCoAs, and subclinical bilateral cochlear dysfunction. The order of magnitude ($\sim 10^{-8}$ to 10^{-9}) estimated for a random association of the described signs would theoretically justify a new clinical entity. Given that the follow-up was systematic, without previous subject selection, it is unlikely that selection criteria could potentially affect data interpretation. However, given that intrauterine mortality for this variant remains unknown, an inevitable selection bias could theoretically be present.

Formation of the external ear is a very complex process, and its careful examination and detailed description may prove to be of diagnostic value in specific syndromes.[25,26] The auricle appears early during embryogenesis, developing from the first and second pharyngeal arches, and can be impacted by any disruptions of its development, as well as by the effects of the intrauterine environment.[27] Although a statistical relationship between abnormal external ear geometry and IUGR/SGA had been suggested previously by our group,[28] the present study indicates that a variant auricle shape is associated with a complex phenotype, thus identifying a previously unrecognized IUGR subset. At this stage of our study, inner ear imaging was not performed. As a consequence, cochlear malformations cannot be ruled out in this particular IUGR/SGA subgroup. However, inner ear congenital malformations are usually found in patients with syndromic sensorineural hearing loss, such as Pendred syndrome,[29,30] although exceptions are known to exist. In particular, patients with complex of enlarged vestibular aqueduct, Mondini dysplasia, large vestibule, and semicircular canal dysplasia usually present with fluctuating hearing loss (93%).[31] This was obviously not the case in our described SGA-variant phenotype, whereas the hearing "abnormality" observed in our SGA-variant subjects, that is, the presence of notches at DPOAEs, was subclinical at the time of examination.

As the pharyngeal arches develop during the fourth week, they are supplied by arteries, the aortic arches, and the distal parts of the third pair of aortic arches join with the dorsal aortae to form the internal carotid arteries, which supply the ears, orbits, and brain. The PCoAs arise from the dorsal aspect of the intracranial internal carotid artery, run caudally and medially, and, finally, join to the PCA, forming an important connection between the carotid and vertebrobasilar circulations.[32,33] Therefore, the associated abnormalities of the external ear and the PCoAs could be considered as the result of an aberrant development of the mesoderm of the pharyngeal arches.

The occurrence of notches at the DPOAEs in children with the phenotypical SGA variant indicates a subclinical impairment of the outer hair cell function. The mean peak frequencies of the notch at middle-high frequencies in both children with the IUGR/SGA variant and their mothers are compatible with a subclinical dysfunction of the intermediate-basal gyrus of the cochlea. The internal ear develops in the fourth week from the surface ectoderm: the hair cells are specified from the simple epithelium of the early otic vesicle, deriving probably from the same common progenitor of the supporting cells through appropriate cell-cell contacts.[34] Thus, the subclinical cochlear dysfunction here observed may likely reflect a primary disturbance of these mechanosensory cells.

The observed changes in skin texture, associated with increased skin softness and macroscopic changes in the stratum corneum, add to previous findings of subtle, permanent skin markers in children with a history of impaired fetal growth. In particular, a relationship among IUGR, fingerprints pattern abnormalities, shape of the palm, and hypertension had been reported previously.[5] On the other hand, joint hypermobility, a common benign condition (10%–15% in the Western population) of unknown pathogenesis[35] has been related previously to infantile hypertrophic pyloric stenosis,[36] as well as to genetic disorders involving the extracellular matrix (ECM).[37] The coexistence of joint hypermobility and skin abnormalities in SGA children with nonfunctional PCoAs suggests a possible involvement of ECM, although at this stage there is no definite proof for either a previously recognized or undescribed collagen disorder in this subgroup of SGA subjects.

The relatively spared head growth at birth shown by the SGA-variant subjects suggests a form of "primary" IUGR as opposed to the IUGR mostly "secondary" to maternal pregnancy-induced hypertension/preeclampsia of the control group. As a consequence, IUGR should be considered as an adverse effect by a fetoplacental pathology on the intrauterine growth for a fetus with a normal growth target as opposed to a preprogrammed

lower size in the "primary" (ie, variant) form described here. By contrast, the observed female prevalence and the close similarity between some of the phenotypical features of SGA-variant children and those of their mothers (ie, auricle helix change, low hemodynamical responses of the PCoAs, and subclinical cochlear dysfunction) remain unexplained at this time, while raising the possibility of inherited traits.

Considering all of these features, the phenotype of the described IUGR/SGA variant is likely the consequence of a large, developmental disturbance occurring early in embryogenesis. In addition, it should be noted that this multiple developmental disorder seems to be generally benign, although no data exist on the intrauterine mortality rate in the proposed phenotypical variant. If we consider the skin, reciprocal epithelial-mesenchymal interactions could coordinate a common developmental program, and its disturbance can determine disorders with defects in multiple organs (ie, pleiotropy). In this context, the ECM could play a primary role, containing a diversity of molecules interacting with each other, as well as with epithelial and mesenchymal cells via specific cell-surface molecules (integrins).

The precise molecular defects underlying the observed clinical phenotype are difficult to be predicted at this stage of knowledge. In IUGR complex genetic mechanisms, such as uniparental disomy[38] or epigenetic changes[39] seem to be involved in generating different subtypes. In our series, the absence of familial cases makes it unlikely a single gene/monogenic Mendelian inheritance model, whereas suggesting the role of more complex genetic/environmental mechanisms in determining phenotypic features. The use of new, more refined molecular investigation techniques, such as comparative genomic hybridization genomics and telomeric array, could provide interesting clues for a better understanding molecular pathogenesis of the condition described in our patients. Additional studies are also needed to explore the frequency and geographic distribution of the observed IUGR/SGA variant, as well as its possible relationships with long-term prognosis and other possible markers of fetal programming.

REFERENCES

1. Dogra VS, Bhatt S. Intrauterine growth retardation. Available at: www.emedicine.com/radio/topic364.htm. Accessed July 21, 2005
2. Barker DJ, Lackland DT. Prenatal influences on stroke mortality in England and Wales. *Stroke.* 2003;34:1598–602
3. Barker DJ. Developmental origins of adult health and disease. *J Epidemiol Community Health.* 2004;58:114–115
4. Latini G, De Mitri B, Del Vecchio A, Chitano G, De Felice C, Zetterstrom R. Abdominal organ growth in intrauterine growth retardation: fetal "programming" causing "metabolic syndrome" in adult age. *Acta Paediatr.* 2004;93:1635–1639
5. Godfrey KM, Barker DJ, Peace J, Cloke J, Osmond C. Relation of fingerprints and shape of the palm to fetal growth and adult blood pressure. *BMJ.* 1993;307:405–409
6. Manning JT, Callow M, Bundred PE. Finger and toe ratios in humans and mice: implications for the aetiology of diseases influenced by HOX genes. *Med Hypotheses.* 2003;60:340–343
7. Ronalds G, Phillips DI, Godfrey KM, Manning JT. The ratio of second to fourth digit lengths: a marker of impaired fetal growth? *Early Hum Dev.* 2002;68:21–26
8. Parazzini F, Cortinovis I, Bortolus R, Fedele L. *Standards of birth weight in Italy [in Italian] Ann Ostet Ginecol Med Perinat.* 1991; 112:203–246
9. Cacciari E, Milani S, Balsamo A, et al. Italian cross-sectional growth charts for height, weight and BMI (6–20 y). *Eur J Clin Nutr.* 2002;56:171–180
10. Ehrenberg HM, Dierker L, Milluzzi C, Mercer BM. Low maternal weight, failure to thrive in pregnancy, and adverse pregnancy outcomes. *Am J Obstet Gynecol.* 2003;189:1726–1730
11. Strambi M, Vezzosi P, Buoni S, Berni S, Longini M. Blood pressure in the small-for-gestational age newborn. *Minerva Pediatr.* 2004;56:603–610
12. Menghetti E, Virdis R, Strambi M, et al. Blood pressure in childhood and adolescence: the Italian normal standards. Study Group on Hypertension' of the Italian Society of Pediatrics'. *J Hypertens.* 1999;17:1363–1372
13. Palmer AR, Strobeck C. Fluctuating asymmetry: measurement, analysis and pattern. *Annu Rev Ecol Syst.* 1986;17:391–421
14. Baumgartner RW. Transcranial color duplex sonography in cerebrovascular disease: a systematic review. *Cerebrovasc Dis.* 2003;16:4–13
15. Hoksbergen AW, Majoie CB, Hulsmans FJ, Legemate DA. Assessment of the collateral function of the circle of Willis: three-dimensional time-of-flight MR angiography compared with transcranial color-coded duplex sonography. *Am J Neuroradiol.* 2003;24:456–462
16. Newell DW, Aaslid R. *Transcranial Doppler.* New York, NY: Raven Press; 1992
17. Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. *Ann Rheum Dis.* 1973;32:413–418
18. Carter C, Wilkinson J. Persistent joint laxity and congenital dislocation of the hip. *J Bone Joint Surg Br.* 1964;46:40–45
19. Klemp P, Stevens JE, Isaacs S. A hypermobility study in ballet dancers. *J Rheumatol.* 1984;11:692–696
20. Kemp DT. Stimulated acoustic emissions from within the human auditory system. *J Acoust Soc Am.* 1978;64:1386–1391
21. Probst R, Lonsbury-Martin BL, Martin GK. A review of otoacoustic emissions. *J Acoust Soc Am.* 1991;89:2027–2067
22. De Felice C, De Capua B, Tassi R, Mencattini G, Passali D. Non-functioning posterior communicating arteries of circle of Willis in idiopathic sudden hearing loss. *Lancet.* 2000;356:1237–1238
23. De Capua B, De Felice C, D'Onza M, et al. Idiopathic sudden hearing loss: role of the posterior communicating cerebral ar-

teries of the Willis' circle [in Italian]. *Acta Otorhinolaryngol Ital.* 2001;21:144–150

24. Tassi R, De Felice C, De Capua B, et al. Cerebrovascular hemodynamic changes in subjective idiopathic tinnitus [abstract]. *Cerebrovasc Dis.* 2003;16(suppl):25

25. Hunter AGW, Yotsuyanagi T. The external ear: more attention to detail may aid syndrome diagnosis and contribute answers to embryological questions. *Am J Med Genet A.* 2005;135:237–250

26. Bader D, Grun M, Riskin-Mashiah S, et al. Auricular mild error of morphogenesis: epidemiological analysis, local correlations and clinical significance. *Ann Genet.* 2004;47:225–234

27. Spilman L. Examination of the external ear. *Adv Neonatal Care.* 2002;2:72–80

28. Centini G, De Felice C. Abnormal external ear shape: a new clinical sign in idiopathic fetal growth restriction. *Ultrasound Obstet Gyn.* 2004;3:366

29. Strasnick B, Moody Antonio S. Inner ear, syndromic sensorineural hearing loss. Available at: www.emedicine.com/ENT/topic225.htm. Accessed August 30, 2006

30. Yang JJ, Tsai CC, Hsu HM, Shiao JY, Su CC, Li SY. Hearing loss associated with enlarged vestibular aqueduct and Mondini dysplasia is caused by splice-site mutation in the PDS gene. *Hear Res.* 2005;199:22–30

31. Wu CC, Chen YS, Chen PJ, Hsu CJ. Common clinical features of children with enlarged vestibular aqueduct and Mondini dysplasia. *Laryngoscope.* 2005;115:132–137

32. Padget DH. The development of the cranial arteries in the human embryo. *Contrib Embryol.* 1948;32:205–261

33. Padget DH. The circle of Willis, its embryology and anatomy. In: Dandy WE ed. *Intracranial Arterial Aneurysms.* Ithaca, NY: Comstock Publishing Co; 1944:67–90

34. Fekete DM, Muthukumar S, Karagogeos D. Hair cells and supporting cells share a common progenitor in the avian inner ear. *J Neurosci.* 1998;18:7811–7821

35. Vougiouka O, Moustaki M, Tsanaktsi M. Benign hypermobility syndrome in Greek schoolchildren. *Eur J Pediatr.* 2000;159:628

36. De Felice C, Di Maggio G, Toti P, et al. Infantile hypertrophic pyloric stenosis and asymptomatic joint hypermobility. *J Pediatr.* 2001;138:596–598

37. Grahame R. Joint hypermobility and genetic collagen disorders: are they related? *Arch Dis Child.* 1999;80:188–191

38. Kotzot D, Utermann G. Uniparental disomy (UPD) other than 15. *Am J Med Genet A.* 2005;136:287–305

39. Gicquel C, Rossignol S, Cabrol S, et al. Epimutation of the telomeric imprinting center region on chromosome 11p15 in Silver-Russel syndrome. *Nat Genet.* 2005;37:1003–1007

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