IGF1R GENE ALTERATIONS IN CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA)

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No conflict of interests.

Introduction

- Small for gestational age children (SGA) are born on term with birth weight (BW) and/or birth length (BL) of -2.0 standard deviation score (SDS).
- The children born small for gestation age have an incidence approximately 5% of all newly births.
- Only 10% of children do not attain normal height until the age of four or five years. In fact, that 10 % have a higher risk to remain short, as well as increased prone to diabetes mellitus, cerebrovascular and cardiovascular diseases in adulthood .
- The etiology of SGA is heterogeneous. Oftentimes defects of IGF1R are the cause of SGA. Most frequently affected part of the *IGF1R* gene is the exon 2.
- The aim of this study** - to investigate whether the exon 2 of the *IGF1R* gene is affected in the SGA children.

Abstract

Background and Aims: Small for gestational age children (SGA) are born on term with BW and or BL of -2.0 SDS. SGA children have an increased risk of being short, developing DM, and cardiovascular and cerebrovascular disease. Oftentimes defects of IGF1R are the cause of SGA. Most frequently affected part of the *IGF1R* gene is the exon 2.

Methods: A cohort of 100 SGA children born in term was evaluated for alterations in *IG1R* gene. Their anthropometric parameters, IGF1 serum concentrations and IGF1 SDS values were analysed. The molecular analysis of *IGF1R* gene was performed by PCR restriction-site analysis and followed by direct sequencing of conspicuous fragments.

Results: Within our cohort, 64 SGA children were with short stature (height SDS -3.25±0.90 SDS) and 36 were with normal height for their age and sex, (H SDS was 0.20±1.1 SDS). None of these children had microcephaly (ocipitofrontal circumference -0.70±1.01SDS vs. 0.06±0.56SDS in SGA children with normal height) or dysmorphic features. The IGF1 serum concentrations and IGF1 SDS values of all children were within normal range. Only one child had lower normal serum IGF1 concentration. No alterations in exon 2 of *IGF1R* gene were detected.

Conclusions: The genetic analysis of the exon 2 of the *IGF1R* gene did not detect any gene defects in the analysed patients. The putative genetic defect in those children affects other parts of the IGF1R gene or other gene(s), or yet unidentified factors.

Key words: SGA born children, microcephaly, short stature, exon 2 of *IGF1R* gene, gene analysis

Methods

- The cohort of **100 (M:F = 40:60) SGA children born in term (≥ 37 GW):**
 - a group of **64** SGA born children (> 4 years) **with short stature** and
 - a group of **36** SGA born children (> 4 years) **with normal growth spurts;**
- AGA (appropriate for gestational age) born children - control group (≥ 37 GW):**
 - a group of **35** children **with normal growth spurts;**

- Anthropometrical data were:**
 - ✓ height standard deviation score (SDS), weight SDS, body mass index (BMI in kg/m²), BMI z score, ocipitofrontal circumference.
- Clinical birth data was evaluated by:**
 - ✓ birth length (BL), birth weight (BW), BL SDS and BW SDS and Gestational age in weeks (GW);
- The serum concentrations of IGF1 were determinated by:**
 - ✓ Chemi-luminescence immune assay method (IMMULITE 2000 Siemens, Immunoassay System apparatus);
- The molecular analysis of IGF1R gene was performed by:**
 - ✓ PCR restriction-site analysis and followed by direct sequencing of conspicuous fragments.

Results

- AGE**
 - ✦ Short SGA born children - 7.42 y ± 3,41 SDS;
 - ✦ SGA born children with normal height – 7,20 y ± 3,26 SDS;
 - ✦ AGA born children - 10,48 y ± 4,17 SDS;
- ✦ No dysmorphic features in SGA born children

GROUPS		short SGA children		SGA children with normal height		Comparison between two groups
PARAMETERS		mean	p-value from KS test	mean	p-value from KS test	p-value
PARAMETERS	BW	2284.37±433 SDS	0.18	2502.5±317.8 SDS	0.97	0.0095
	BW SDS	-2.7111±0.5 SDS	0.78	-2.1515±0.56SDS	0.48	0.0009
	BL	47.06±2.09 SDS	0.56	46.63±2.12 SDS	0.87	0.33
	BL SDS	-1.33±1.03 SDS	0.34	-1.61±1.12 SDS	0.93	0.22
	GW	39.17±0.94 SDS	0.46	39.34±0.90 SDS	0.61	0.37
Patients		M	n= 31		n= 23	
		F	n= 33		n= 23	

GROUPS		short SGA children		SGA children with normal height		Comparison between two groups
PARAMETERS		mean	p-value from KS test	mean	p-value from KS test	p-value
H SDS	-	-3.25±0.90 SDS	0.19	0.20±1.1 SDS	0.62	0.024
W SDS	-	-2.72±1.39 SDS	0.45	0.29±1.53 SDS	0.65	3.30e-16
BMI	kg/m ²	15.25±2.15 SDS	0.41	17.28±4.39 SDS	0.14	0.012
BMI z-score	-	-0.88±1.78 SDS	0.31	0.01±1.68 SDS	0.70	0.015
OFC SDS	-	-0.70±1.01 SDS	0.91	0.06±0.56 SDS	0.95	3.82e-06
TH SDS	-	-1.00±0.87 SDS	0.52	0.15±0.91 SDS	0.98	6.98e-9

- ✦ The PCR restriction-site analysis in all SGA born children did not show any genetic alteration in exon 2 of *IGF1R* gene.
- ✦ The screened PCR products coding *IGF1R* exon 2 by direct sequencing of conspicuous fragments were uneventful.

Discussion

- Several alterations (point mutations and deletions) in the *IGF1* and insulin-like growth factor 1 receptor (*IGF-1R*) genes have been demonstrated last decade.
- Alterations have been identified that affect IGF1R biosynthesis, signal reception and receptor kinase activity;
- Homozygous defects in the *IGF1* gene have been found in patients with major developmental impairments and severe intrauterine and postnatal growth retardation.
- The mutations in *IGF1R* gene that have been predominantly heterozygous are 3 found in patients with mild phenotype and clinically heterogeneous presentation;
- Abuzzahab et al 2003y.: 2 point mutations in exon 2 of *IGF1R* gene: compound heterozygosity (p. R108Q) and (p. K115N) in SGA born girl with delayed motor development, psychiatric problems and growth retardation.
- Abuzzahab et al 2003y: another heterozygous mutation in the exon 2 (p. R89X) in an IUGR born boy with microcephaly, short stature and delayed motor and speech development.

Conclusions

- Within a cohort of 100 SGA born children without microcephaly or dysmorphic features we did not find alterations in the exon 2 of the *IGF1R* gene.
- Exon 2 of the *IGF1R* gene might not be a hotspot for alterations.
- The putative genetic defect in those children affects other parts of the IGF1R gene or other gene(s), or yet unidentified factors.