Ophthalmological findings in children and adolescents with Silver Russell Syndrome

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ABSTRACT

Aim: To evaluate ophthalmological findings in children with Silver Russell Syndrome (SRS).

Methods: An ophthalmological evaluation including visual acuity (VA), refraction, strabismus, near point of convergence (NPC), slit-lamp examination, ophthalmoscopy, axial length measurements, and full-field electroretinogram was performed on 18 children with SRS (8 girls, 10 boys; mean age 11.6 years). Fundus photographs were taken for digital image analysis. Data were compared with data on an age- and gender-matched reference group (ref) of school children (n=99).

Results: Seventeen out of 18 children with SRS had ophthalmological abnormalities. Best corrected VA of the best eye was <0.1 log of the minimal angle of resolution in 11 children (ref n=98) ($p<0.0001$), and 11 children had refractive errors (ref n=33) ($p=0.05$). Anisometropia (≥1D) was noted in three of the children (ref n=3) ($p=0.046$). Subnormal stereo acuity and NPC were found in 2/16 (ref=0) ($p=0.02$). The total axial length in both eyes was shorter compared with that in controls ($p<0.006$ and $p<0.001$). Small optic discs were found in 3/16, large cup in 3/16, and increased tortuosity of retinal vessels in 4/13 children with SRS.

Conclusion: Children with SRS, who are severely intra-uterine growth-retarded, show significant ophthalmological abnormalities. Based on our findings, we recommend ophthalmological examination in children with SRS.

INTRODUCTION

Silver Russell Syndrome (SRS) is a rare syndrome characterized by pre- and postnatal growth retardation, a triangular face, micrognathia, lateral asymmetry, and clinodactylia (Fig. 1A).[1] So far, little is known about the cause of the disease, although several genetic abnormalities have been described involving chromosomes 1, 7, 8, 11, 15, 17, and 18.[2–3] Today we know that a large proportion of children with SRS have either hypomethylation at the imprinting control region of chromosome 11p15 (30–65%) with a more severe phenotype [4] or maternal uniparental disomy of chromosome 7 (5–10%) with a milder phenotype.[4–5] The candidate genes are those imprinted in the regions of chromosomes 7 and 11, such as insulin-like growth factor 2 (IGF2), IGF2 receptor (IGF2R), and growth factor receptor-bound protein 10 (Grb 10).

Different ophthalmological findings, such as ptosis, epicanthal folds, hypertelorism, long eyelashes, eyebrows meeting in the midline, protruding eyeballs, microphthalmia, strabismus, blue sclera, absence of the lacrimal duct, microcornea, heterochromia, myopia, subnormal visual acuity (VA), cataract, asymmetry and central excavation of the optic discs, pigmentary retinopathy, retinal detachment, decreased full-field electroretinogram (ERG) potential, and congenital glaucoma, have previously been described in separate case reports in patients with SRS.[6–8]

However, to our knowledge, no detailed ophthalmological investigation in a larger number of patients with SRS has previously been reported. Therefore, the purpose of this study was to prospectively evaluate visual function and ocular findings in patients with SRS, a group born extremely small for gestational age (SGA).

MATERIALS AND METHODS

Patients

Eighteen children and adolescents (8 girls, 10 boys; mean age 11.6 years, range 3.4–18.1 years) fulfilling all criteria for the diagnosis of SRS were referred from across Sweden and examined by a national multidisciplinary team at the Queen Silvia Children's Hospital, Gothenburg, Sweden. Table 1 shows auxological data at birth and proportion of preterm births in the children with SRS. Birth weight and birth length were converted into standard deviation scores (SDSs) based on Swedish reference values.[9] The mean birth weight SDS was -3.1 (range -1.2 – -4.5) and the mean birth length SDS was -3.2 (range 0 – -5.6); all of these children were SGA by birth weight, birth length, or both. At the time of the investigation, 16 of the 18 children had been treated with growth hormone (GH) for a mean period of 6.6 years (range 2–14 years).

Table 1.

	SRS group (n=18*)	**Reference group (n=99*)**
Birth weight (g) Mean (range)	1,880 (1,164–2,890)	3,590 (1,540–4,890)
Birth length (cm) Mean (range)	42 (34–48) (n=17)	50 (40–57)
Head circumference (cm) Mean (range)	32 (28.5–34) (n=11)	33.6 (31–38.5) (n=98)
Gestational age (wks) Mean (range)	37 (33–41)	39.6 (35–42)
Preterm birth (<37 wks GA) n (%)	9 (50.0%)	3 (3.0%)

*Where numbers differ from the number of children in the group, they are given separately for each category. GA = gestational age; SRS = Silver Russell Syndrome.

Reference group

Ophthalmological data were compared with data for an age- and sex-matched reference group (ref) of Swedish school children (n=99, 54 girls and 45 boys, mean age 11.5 years [range 7.4–15.9 years]) tested under identical conditions as the study cohort.[10] Auxological data at birth are presented in Table 1. Another 99 healthy Swedish children and adolescents (56 boys, 43 girls) aged between 3 and 19 (mean age 10.1 years) and born at term constituted a reference group for evaluation of ocular fundus morphology.[11]

Methods

A detailed ophthalmological evaluation was performed, including:

1. Determination of best corrected visual acuity for near and distant fixation

Best corrected VA (BCVA) was tested with a linear KM-Boks chart.[12] For children who could not read the KM-Boks chart, we used the HOTV chart. Distance VA was tested monocularly at a distance of 3 m and near vision was tested binocularly at a distance of 0.33 m.

2. Refraction under cycloplegia

Refraction tests were performed with an autorefractor (Topcon A6 300, Topcon Corporation, Tokyo, Japan) after a single instillation of a mixture of cyclopentolate (0.85%) and phenylephrine (1.5%). Significant refractive errors were defined as the spherical equivalent (SE) of ≥0.5 dioptre (D) for myopia or ≥2.0 D for hyperopia. Astigmatism was assessed at a level of ≥0.75 D SE, and anisometropia at ≥1.0 D SE.

3. Investigation of strabismus and ocular motility

Heterotropia, defined as intermittent or constant, near (0.33 m) or at distance (3 m), was diagnosed with cover–uncover tests. Heterophoria was diagnosed with alternate cover tests, and deviations were quantified using alternate prism cover tests. Exophoria was defined as values below the 5^{th} percentile in the control group (negative values), and esophoria as values above the 95^{th} percentile (positive values). Thus, the cut-off values defining significant heterophoria were between <-2 and >0 prism dioptres (pD) for distance and between <-10 and >0 pD for near vision. Motility was assessed with a penlight and described in terms of over- or under-functioning.

4. Testing of stereo acuity

Stereo acuity was tested with the TNO random dot stereo test, the Lang I stereo card, or the Titmus test, as appropriate. Subnormal stereo acuity was defined as >60 seconds of arc.

5. Near point of convergence

Near point of convergence (NPC), in cm, was measured three times with a Royal Air Force ruler and the mean value of the measurements was recorded.

6. Fixation recordings

The simultaneous horizontal and vertical positions of the right and left eye were recorded using the Orbit infrared (IR) system (IOTA Inc, Timrå, Sweden). In this IR device, pulsed infrared light, emitted inside a pair of goggles, is reflected against the ocular surface and detected by eight detectors. Eye position signals are conducted via a sound card to a computer, where they are recorded. The investigation is described in detail elsewhere.[13]

7. *Assessment of ocular dimensions*

The medial intercanthal distance (ICD) and right and left palpebral fissure lengths (PFLs), in mm, were measured with a ruler. Total axial length (TAL) was measured by ultrasound biometry (Paxis, version 2.01; BIOVISION, Clermont-Ferrand, France).

8. Examination of the anterior segment, media, and ocular fundus

Examination of the anterior segment of the eye was performed with a slit lamp and the ocular fundus was examined by indirect ophthalmoscopy.

9. Electroretinogram

A full-field ERG of one eye was recorded using a bipolar contact lens in a Nicolet Analysis System (Nicolet Biomedical Instruments, Madison, WI, USA) as described elsewhere,[14] according to International Society for Clinical Electrophysiology of Vision standards.[15] In some cases, skin electrode ERGs were registered. This involved placing a silver–silver chloride electrode just below the central lower lid margin. A single flash, using a red filter, with a Grass flashlight stimulus of supramaximal intensity (<100 μs, ~0.5 J) was projected at a distance of approximately 20 cm to the child's eye.

10. Photography of the ocular fundus for quantitative digital image analysis

Ocular fundus photographs taken in cycloplegia were analysed with a specially designed computer-assisted digital mapping system [16] in regard to the optic disc area (ODA), optic cup area, neuroretinal rim area, tortuosity of veins and arteries, and number of branching points.

Statistical analysis

Means, standard deviations (SDs), medians. and ranges were calculated for descriptive purposes. For a comparison between two groups, Mann-Whitney's U-test was used for ordered and continuous variables; for dichotomous variables, Fisher's exact test was used. Test results were considered to be significant at values of $p<0.05$. The reference group for this study was selected individually by minimizing the maximal *t*-values over the variables age and sex between the group of children with SRS and a reference group of 143 healthy, Swedish school-aged children.[10]

Ethical approval

The study was approved by the Ethical Committee at the Medical Faculty, Sahlgrenska Academy at the University of Gothenburg, Sweden. Informed consent was obtained from the parents of all the children participating in the study.

RESULTS

Altogether, 17/18 children with SRS had ophthalmologic abnormalities. Table 2 summarizes the ophthalmological findings in each of the 18 children and youths with SRS.

Table 2.

Case/sex/ age (yrs) **and if treated with GH** (+/-)	**Visual acuity** logMAR OD/OS	**Refraction** Sph/cyl OD OS	**Aniso-metropia** >1D SE	**Strabismus/ ocular motility**	**Stereo Acuity** (’’)/ **NPC** (cm)	**Anterior segment/ media/fundus**
1/M/17/+	0.1/0.1†	+6.50/-0.50 +6.25/-0.5	–	NA	NA	Small ODA
2/F/3/-	0.2/0.2*	+2.25/-0.25 +3.50/-0.25	+	Orthophoria	240’’ 6 cm	‡, abnormal lashes
3/M/9/+	0.05/0.2 †	+0.25/-0.75 +0.75/-1.75	–	Esotropia	1,200’’ 6 cm	‡, ptosis, epicanthal folds, abnormal eyebrows, large cup, small rim area
4/F/8/+	0.1/0.1†	+1.0/-0.50 +1.25/-0.50	–	Exophoria	60’’ 6 cm	Large cup, tortuosity of retinal vessels
5/F/14/+	0.0/0.0†	-0.5/-1.25 -1.0/-0.25	–	Exophoria, NPC >6 cm	30’’ 6 cm	
6/M/12/+	0.0/0.0†	+2.75/-1.25 +4.50/-1.75	+	Exotropia	60’’ 20 cm	‡, abnormal eyebrows and lashes, small ODA, small rim area
7/F/15/+	- 0.1/0.0†	+1.0/-0.25 +1.25/-0.50	–	Esophoria	60’’ 6 cm	‡, abnormal lashes
8/M/8/+	0.2/0.3	+1.5/-0.5 +1.25/-1.50	–	Orthophoria, underaction of both LR	60’’ 6 cm	‡, abnormal lashes, ODAs >0.8 mm diff
9/M/18/+	0.0/- 0.1†	-1.0/-1.75 -1.0/-1.0	–	Orthophoria, NPC >6 cm	60’’ 10 cm	Abnormal eyebrows
10/M/12/+	0.0/0.0	+0.25/-0.75 +0.50/-0.25	–	Exophoria	30’’ 6 cm	Small rim area
11/M/13/+	0.0/0.0†	-3.50/-1.50 -3.50/-1.50	–	Orthophoria	60’’ 6 cm	Large cup
12/M/13/+	0.0/0.0	+1.5/-0.25 +0.5/-0.25	+	Orthophoria	30’’ 6 cm	Abnormal eyebrows, small ODA
13/F/10/+	0.1/0.1	+1.0/-0.50 +0.75/-0.25	–	Orthophoria	60’’ 6 cm	Tortuosity of retinal vessels
14/F/15/-	0.05/0.2	-1.5 -1.0/-0.75	–	Esophoria	240’’ 6 cm	
15/M/9/+	0.3/0.3†	+0.50/-0.25 +0.50/-0.50	–	Esotropia, overaction of both IOs	100’’ neg	‡, tortuosity of retinal vessels
16/F/10/+	0.1/0.1	+0.25 +.25/-0.25	–	Exophoria	60’’ 6 cm	
17/M/12/+	0.0/0.0	+-0/-0.50 +0.25/-0.50	–	NA	NA	ODAs >0.8 mm diff
18/F/12/+	0.0/0.0	+1.5/-0.25 +1.75/-0.5	–	Orthophoria	15’’ 6 cm	‡, tortuosity of retinal vessels

*The HOTV chart was used; †wearing glasses; ‡intercanthal distance (ICD) ≥5–10 mm ≥ palpebral fissure length (PFL); + = yes; – = no; ” = seconds of arc.
cyl = cylindrical; D = dioptre; diff = difference; F = female; GH = growth hormone; IO = inferior oblique muscle; logMAR = log of the minimal angle of resolution; LR = lateral recti; M = male; NA = not available; neg = negative; NPC = near point of convergence; OD = ocular dexter (right eye); ODA = optic disc area; OS = ocular sinister (left eye); SE = spherical equivalent; sph = spherical.

Visual acuity, refraction, strabismus, ocular motility, stereo acuity, and near point of convergence

Table 3 shows BCVA at distance (better eye), near VA (binocular), refractive errors, heterotropia, significant heterophoria, ocular motility, stereo acuity, and NPC in the two groups.

In total, 11/18 children with SRS had refractive errors (ref 33/99) (p=0.05). The median SE in the study cohort was +0.56 (range -4.25–+6.25) for right eyes and +0.31 (range -4.25–+6.125) for left eyes. No statistical difference between right and left eyes was found regarding VA, refraction in SE, or astigmatism in the children with SRS.

Table 3.

Ophthalmological findings n (%)	**SRS group (n=18*)**	**Ref group (n=99*)**	**p-value**
Visual acuity (logMAR) best eye at distance			
≥0.3	1 (5.6%)	0 (0%)	n.s.
0.2–0.1	6 (33.3%)	1 (1.0%)	<0.0001
<0.1	11 (61.1%)	98 (99.1%)	<0.0001
Visual acuity (logMAR) binocular at near range			
≥0.3	1 (6.7%); n=15	0 (0%)	n.s.
0.2–0.1	2 (13.3%); n=15	0 (0%)	0.04
<0.1	12 (80.0%); n=15	99 (100%)	0.004
Refraction			
myopia (≥0.5 D SE)	4 (22.2%)	9 (9.1%)	n.s.
hyperopia (≥2.0 D SE)	3 (16.7%)	5 (5.1%)	n.s.
astigmatism (≥0.75 D)	8 (44.4%)	25 (25.3%)	n.s.
anisometropia (≥1.0 D SE)	3 (16.7%)	3 (3.0%)	0.046
wearing glasses	9 (50.0%)	6 (6.1%)	<0.001
Strabismus heterotropia	3 (18.8%); n=16	3 (3.0%)	n.s.
significant heterophoria at distance	1 (6.3%); n=16	5 (5.1%)	n.s.
significant heterophoria at near	2 (12.5%); n=16	2 (20.2%)	n.s.
Stereo acuity (>60'')†	2 (12.5%); n=16	0 (0%)	0.02
NPC >6 cm†	2 (12.5%); n=16	0 (0%)	0.02

*Where numbers differ from the total number of children in the group, they are given separately for each category; †without having heterotropia.
D = dioptre; logMAR = log of the minimal angle of resolution; NPC = near point of convergence; n.s. = not significant; SE = spherical equivalent.

Fixation

No significant difference between the eyes or between the children with SRS and the controls was found regarding fixation in primary position, i.e. fixation time, number of intruding saccades, drifts, or blinks recorded by the Orbit IR system.

Ocular dimensions

The mean and SDs of ICD, PFL, and TAL of right and left eyes for the children with SRS as well as for the reference group are shown in Table 4. No significant difference between right and left eyes was found regarding PFL and TAL in the children with SRS. An ICD of ≥5–10 mm ≥ PFL was recorded in 7/15 children (ref 10/99) (p=0.002).

Table 4.

Ocular dimensions	**SRS** (n=18)* **Mean (SD)**	**Ref** (n=99)* **Mean (SD)**	**p-value**
ICD (mm)	29.40 (3.36) (n=15)	28.45 (2.23) (n=88)	n.s.
PFL (mm) OD	25.38 (2.55) (n=16)	26.32 (1.89) (n=88)	n.s.
PFL (mm) OS	25.25 (2.59) (n=16)	26.48 (1.84) (n=88)	0.03
TAL (mm) OD	22.09 (1.07) (n=12)	22.71 (0.68) (n=75)	0.006
TAL (mm) OS	21.96 (1.11) (n=12)	22.76 (0.70) (n=75)	0.001

*Where numbers differ from the number of children in the group, they are given separately for each category.
ICD = medial intercanthal distance; n.s. = non-significant; OD = right eye; OS = left eye; PFL = palpebral fissure length; SD = standard deviation; SRS = Silver Russell Syndrome; TAL = total axial length.

Examination of the anterior segment, media, and ocular fundus

Abnormal growth of the eyebrows was recognized in four children with SRS and four had long, full prominent lashes bilaterally. Epicanthal folds and unilateral ptosis were seen in one child (Table 2).

Electroretinogram

Electroretinogram was performed in 16 children with SRS, in 11 of whom skin-electrode ERG was performed, while 5 underwent full-field ERG. The retinal conditions showed normal activity in all children.

Digital image analysis

Ocular fundus photographs of 16 children were analysed with regard to the ODA, cup area, and neuroretinal rim area. Tortuosity of veins and arteries and number of branching points were analysed in 13 children.

Optic disc morphology

Of 16 children, 3 had an ODA and 3 had a neuroretinal rim area that was smaller than the 5^{th} percentile for the controls (<1.82 mm^2 and <1.52 mm^2, respectively) (Table 2; Fig. 1B). Three children had a cup area larger than the 95^{th} percentile for the controls (>0.79 mm^2) (Table 2). There was no significant difference in optic disc, cup, or rim area between the two groups. However, there was a tendency towards larger cups in children with SRS (median 0.56; range 0.0–1.20) than in controls (median 0.34; range 0.0–1.61) (p=0.056). No significant difference between right and left eyes regarding optic disc, cup, or rim area was found.

Retinal vessel morphology

Two out of 13 children with SRS had an increased tortuosity of arteries (ITA), and four children had an increased tortuosity of veins (ITV) above the 95th percentile for the controls (>1.17 and >1.09, respectively) (Table 2; Fig. 1C). Five children with SRS had a decreased number of central vascular branching points below the 5th percentile for the controls (<21) (see Fig. 1C). However, no significant difference was found in ITA, ITV, or number of branching points between the two groups.

DISCUSSION

The children and adolescents with SRS in this prospective study showed a high number of visual and ocular abnormalities, such as subnormal VA, refractive errors, anisometropia, subnormal stereo acuity, and subnormal NPC, as well as short eyes compared with controls. In addition, ptosis, epicanthal folds, long eyelashes, eyebrows meeting in the midline, hypertelorism, small optic discs, large cups, and increased tortuosity of retinal vessels were seen in some of the children.

Children with SRS commonly show a lateral facial and/or skeletal asymmetry. In an interesting case report presented by Siegel *et al* (1998), an asymmetry of the optic discs was demonstrated in a child with SRS.[7] A 0.6 mm difference between the optic discs was measured biomicroscopically using a 78 D-ruled indirect lens. Two of the children in our study (cases 8 and 17) also showed a difference of optic disc size (0.88 mm), as measured by the digital analysing system used in this study (Table 2). However, for the group as a whole, no significant difference between the sizes of the right and left optic discs could be found. On the other hand, we found that anisometropia (≥1.0 D SE), reflecting an asymmetric disorder, was more common in children with SRS than in controls (Tables 2 and 3). This finding has

not previously been reported in children with SRS. In addition, three children (cases no 3, 5, and 8) have an astigmatism with ≥1.0 D difference between the eyes (Table 2). Knowledge of an asymmetry of refraction is important for the development of the child's visual function and for preventing anisometric amblyopia.

Growth hormone and insulin-like growth factor 1 (IGF-1) are involved in ocular growth by influencing the synthesis of the extracellular matrix of the sclera and by inducing angiogenesis.[17] An association between optic nerve hypoplasia and reduced retinal vascularization, as well as a mean hyperopic defect related to shorter axial length and an increased central corneal thickness, is documented in individuals with GH deficiency.[17–19] At the time of this investigation, 16 children with SRS were being treated with GH, three of whom had small optic discs as measured by the digital analysis system. Interestingly, despite being treated with GH, these children still had significantly shorter TALs than the controls. Overall, however, their emmetropization seemed to process normally. Parentin and Perissutti (2005) hypothesized, in their study on the effect of GH therapy on refraction, that correct and well-timed substitutive GH therapy could permit normal emmetropization.[20] It can only be speculated whether the change in refraction is related to the GH-induced somatic growth per se, or whether it is a direct effect of GH and/or IGF-1. Further studies are needed regarding the effects of GH replacement therapy on the development of the visual and ocular system.

Abnormal optic nerve and retinal vascular morphology, i.e. reduced rim area and decreased number of central branching points, have previously been reported in young adults who were IUGR infants.[21–22] In the present study, 3/16 children had a reduced rim area and 5/13 children had a decreased number of branching points. A decrease in the neuroretinal rim area reflects either a decrease in the number of axons or a reduction in axonal volume in the optic

disc. The underlying mechanisms and the importance of the decreased number of central branching points are not known.

It is known that humans who have been undernourished during gestation become less healthy later in life.[23] Several studies have shown that prenatal exposure to famine is associated with cardiovascular risk factors and coronary heart disease, brain abnormalities, affective disorders, and antisocial behaviour.[24–25] Children with SRS are a heterogeneous group with different genetic backgrounds.[2] Though they exhibit different severity, however, they all share the same general phenotype and have all had both *in utero* and postnatal growth retardation. Whether it is the genetic background or the foetal milieu per se which has an adverse impact in these children is not known. Children with SRS are found to have impaired growth early in gestation, and this would probably affect several organs, including the brain and the eyes. Besides the ophthalmological impact, as described here, we hypothesize that perception and brain function may also be impaired. It is therefore of great interest to evaluate further the visual perception and other cognitive functions of children with SRS.

In conclusion

On the basis of our findings, we recommend that an ophthalmological examination be performed in children born with severe IUGR, and especially in children with SRS, to optimize the visual and ocular development of these children.

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REFERENCES

1 Rossignol S. Silver-Russell syndrome and its genetic origins. *J Endocrinol Invest* 2006;**29**:9–10.

2 Abu-Amero S, Monk D, Frost J, et al. The genetic aetiology of Silver-Russell syndrome. *J Med Genet* 2008;**45**:193–9.

3 Rossignol S, Netchine I, Le Bouc Y, et al. Epigenetics in Silver-Russell syndrome. *Best Pract Res Clin Endocrinol Metab* 2008;**22**:403–14.

4 Bruce S, Hannula-Jouppi K, Peltonen J, *et al.* Clinically distinct epigenetic subgroups in Silver-Russell syndrome: the degree of H19 hypomethylation associates with phenotype severity and genital and skeletal anomalies. *J Clin Endocrinol Metab* 2009;**94**:579–87.

5 Preece MA, Price SM, Davies V, et al. Maternal uniparental disomy 7 in Silver-Russell syndrome. *J Med Genet* 1997;**34**:6–9.

6 Kass MA, Howard RO, Silverman JP. Russell-Silver dwarfism. *Ann Ophthalmol* 1976;**8**:1337–9.

7 Siegel LM, Granet DB, Jones KL. Optic nerve asymmetry in a child with Russell-Silver syndrome. *Am J Med Genet* 1998;**75**:223–5.

8 Kato R, Kishibayashi J, Shimokawa O, *et al.* Congenital glaucoma and Silver-Russell phenotype associated with partial trisomy 7q and monosomy 15q. *Am J Med Genet* 2001;**104**:319–22.

9 Albertsson Wikland K, Luo ZC, Niklasson A, *et al.* Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. *Acta Paediatr* 2002;**91**:739–54.

10 Andersson Grönlund M, Andersson S, Aring E, *et al*. Ophthalmological findings in a sample of Swedish children aged 4–15 years. *Acta Ophthalmol Scand* 2006;**84**:169–76.

11 Hellström A, Svensson E. Optic disc size and retinal vessel characteristics in healthy children. *Acta Ophthalmol* 1998;**76**:260–7.

12 Moutakis K, Stigmar G, Hall-Lindberg J. Using the KM visual acuity chart for more reliable evaluation of amblyopia compared to the HVOT method. *Acta Ophthalmol Scand.* 2004;**82**:547–51.

13 Aring E, Andersson Grönlund M, Hellström A, *et al.* Visual fixation development in children. *Graefes Arch Clin Exp Ophthalmol* 2007;**245**:1659–65.

14 Andréasson S, Ponjavic V, Abrahamson M, *et al.* Phenotypes in three Swedish families with x-linked retinitis pigmentosa caused by different mutations in the RPGR gene. *Am J Ophthalmol* 1997;**124**:95–102.

15 Marmor MF, Zrenner E. Standard for clinical electroretinography (1999 update). *Doc Ophthalmol* 1999;**97**:143–56.

16 Strömland K, Hellström A, Gustafsson T. Morphometry of the optic nerve and retinal vessels by computer-assisted image analysis. *Graef Arch Clin Exp Ophthalmol* 1995; **233**:150–3.

17 Parentin F, Tonini G, Perissutti P. Refractive evaluation in children with growth defect. *Curr Eye Res* 2004;**28**:11–5.

18 Bourla DH, Laron Z, Snir M *et al.* Insulinlike growth factor I affects ocular development: a study of untreated and treated patients with Laron syndrome. *Ophthalmology* 2006;**113**:1197.e1–5.

19 Parentin F, Pensiero S. Central corneal thickness in children with growth hormone deficiency. *Acta Ophthalmol* 2009 Jun 5. [Epub ahead of print].

20 Parentin F, Perissutti P. Congenital growth hormone deficiency and eye refraction: a longitudinal study. *Ophthalmologica* 2005;**219**:226–31.

21 Hellström A, Dahlgren J, Marsal K *et al.* Abnormal retinal vascular morphology in young adults following intrauterine growth restriction. *Pediatrics* 2004;**113**:77–80.

22 Ley D, Marsal K, Dahlgren J *et al.* Abnormal retinal optic nerve morphology in young adults after intrauterine growth restriction. *Pediatr Res* 2004;**56**:139–44.

23 Barker DJ. Fetal programming of coronary heart disease. *Trends Endocrinol Metab* 2002;**13**:364–8.

24 Neugebauer R, Hoek HW, Susser E. Prenatal exposure to wartime famine and development of antisocial personality disorder in early adulthood. *JAMA* 1999;**282**:455–62.

25 Brown AS, Van Os J, Driessens C *et al.* Further evidence of relation between prenatal famine and major affective disorder. *Am J Psychiatry* 2000;**157**:190–5.

LEGENDS

Table 1

Auxological data at birth and number of preterm births in 18 children with Silver Russell Syndrome (SRS) as well as in an age- and sex-matched reference group (n=99).

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Table 2

Ophthalmological findings in the study population, children and adolescents with Silver Russell Syndrome (SRS).

Table 3

Ophthalmological findings, expressed as number (n) and percentage (%), in children with Silver Russell Syndrome (SRS) compared with the reference group.

Table 4

Ocular dimensions, expressed as mean (standard deviation, SD), in children with Silver Russell Syndrome (SRS) and the reference group, respectively.

Figure 1A–C

A. Silver Russell Syndrome (SRS). Photograph showing a 3-year-old girl with SRS, born in gestational week 36 at birth weight 1,550 g (-4.2 standard deviation score, SDS). The prominent forehead, triangular face, micrognathia, small lips, full prominent eyelashes, and the longer intercanthal distance compared with palpebral fissure length are noticeable. At examination her visual acuity was 0.2 logMAR in both eyes and she was hyperopic as well as anisometropic. Her stereo acuity was 240’’.

B. Small optic disc area (ODA). Fundus photograph showing a 15-year-old girl with SRS and a small optic disc. Her birth weight was 1,330 g (-3.4 SDS) and she was born preterm (in gestational week 35) and small for gestational age (SGA). She had been on growth hormone (GH) treatment since age 4. At examination, she showed subnormal VA (0.05/0.2 logMAR), myopia, significant esophoria, and reduced stereo acuity (240’’).

C. Increased tortuosity of arteries (ITA) and veins (ITV), and a decreased number of central vascular branching points. Fundus photograph of a 10-year-old girl with SRS showing increased ITA and ITV, as well as a decreased number of central vascular branching points. She was born in gestational week 36 with a birth weight of 2,060 g (-2.4 SDS). At the time of examination she had been treated with GH for 7.5 years. She had slightly subnormal VA (0.1 logMAR) in both eyes, but otherwise normal ophthalmological status.