Research Paper

Endocrine morbidity in midline brain defects: Differences between septo-optic dysplasia and related disorders

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ABSTRACT

Background: Septo-optic dysplasia (SOD) is a heterogeneous congenital condition. The aim of this study was to investigate the clinical phenotypes of a large cohort of children with SOD, Multiple Pituitary Hormone Deficiency (MPHD) and Optic Nerve Hypoplasia (ONH), with a focus on endocrine testing.
Methods: Retrospective single-centre longitudinal study of children with SOD (n:171), MPHD (n:53) and ONH (n:35). SOD+ and SOD- indicate patients with or without hypopituitarism, respectively.
Findings: All deficits were more frequent and occurred earlier in MPHD than SOD+ [Hazard Ratios (HR): 0·63 (0·45,0·89) for GH, 0·48(0·34,0·69) for TSH, 0·55(0·38,0·80) for ACTH, 0·28(0·11,0·68) for gonadotropins], except Diabetes Insipidus (DI) [HR: 2·27(0·88,5·9)]. Severe hypothalamo-pituitary (H-P) abnormalities were more frequent in MPHD [80·0% vs 41·6%, p<0·0001 for Ectopic Posterior Pituitary (EPP)]. Stalk and PP abnormalities were associated with more severe endocrine phenotypes and placed a subgroup of SOD+ at risk of developing deficits earlier. SOD and ONH shared heterogeneous phenotypes ranging from pubertal delay to precocity and from leanness to extreme obesity, whilst MPHD had GnD and obesity only. Mortality was recorded in 4·2% (6/144) SOD and 3·2% (1/31) ONH, and only in patients with multisystem phenotypes.
Interpretation: More than a single disease, SOD represents a spectrum of malformative conditions involving different brain structures and characterised by a dynamic and sequential nature of endocrine. In contrast, MPHD displays a more homogeneous phenotype of (mainly) anterior pituitary early-onset failure. Stalk and PP abnormalities place a subgroup of SOD+ at a higher risk of early-onset deficits. Additionally, there are striking differences between the SOD and MPHD cohorts in terms of pubertal progression. The shared phenotypes between ONH and SOD could be partly explained by common hypothalamic dysfunction. The differences between the cohorts are important as they may aid in planning management and preventing morbidity by dictating earlier interventions.
Funding: M.C., M.G., and N.I. were supported by the European Society of Paediatric Endocrinology (ESPE) through ESPE Clinical Fellowships.

1. Introduction

Septo-optic dysplasia (SOD), classically defined by the presence of two or more features of the triad optic nerve hypoplasia (ONH), pituitary deficits, and midline brain defects, is a rare condition with an estimated incidence of 10·9/100000 [1]. More recently, in the multicentre study EUROCAT, its prevalence in Europe was calculated to lie between 1.9 and 2.5 per 100,000 births [2]. It is a poorly understood disorder and its diagnostic criteria have been much debated [3]. Significant phenotypic heterogeneity is observed, even within families [4]. Causative mutations in genes implicated in pituitary development are identified in < 10% of cases [5], thus suggesting a potential role for other genes and/or environmental/epigenetic factors. [6] Given its rarity, the phenotype of this condition has not, to date, been clearly characterised [1,6−15].

The aim of our study was to describe the endocrine morbidity and mortality of a large cohort of children and adolescents with SOD

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Research in context

Evidence before this study

Septo-optic dysplasia (SOD) is a highly heterogeneous congenital condition, and its defining criteria have been much debated. We performed a literature search focused on its endocrine morbidity and mortality on PubMed databases. Limited data were available from small case series, with some relatively larger cohort studies performed on children with isolated hypopituitarism and, more recently, focusing on the onset of pituitary dysfunction in children with optic nerve hypoplasia (ONH). No large-scale data were found comparing the endocrine morbidity in children with isolated hypopituitarism (MPHD) and those with associated midline brain/optic nerve abnormalities (SOD), and those with isolated ONH. and trying to look at all these conditions as a spectrum of the same disease. There was a paucity of data with respect to the evolution of pituitary deficits over time and the pubertal phenotypes of these children, reflecting a considerable gap in our knowledge and understanding of the conditions. Additionally, no mortality data were available in cohorts with these congenital disorders.

Added value of this study

By providing a long-term longitudinal detailed characterisation of the endocrine morbidity and mortality of the largest cohort of children with SOD and related disorders described to date, this study significantly advances our understanding of these conditions. The comparison between patients with different hypothalamo-pituitary and midline brain/optic nerve phenotypes allowed the identification of striking differences among groups, which may aid in planning management and preventing morbidity by dictating the application of earlier interventions. Whilst SOD is a very heterogeneous disease, particularly with respect to the type and onset of pituitary deficits, MPHD has a more homogenous phenotype of (mainly) early-onset anterior pituitary failure, although we have shown that posterior pituitary failure leading to diabetes insipidus may be an evolving feature in some cases. We have documented that specific neuroimaging abnormalities predispose a subgroup of SOD patients to a higher risk of early onset pituitary hormone deficiencies. Shared pubertal and body weight phenotypes are identified between children with ONH and SOD, whilst midline brain abnormalities do not correlate with the endocrine morbidity of these patients. Premature mortality was recorded only in patients with ONH and complex multisystem phenotypes, but not in patients with isolated MPHD.

Implications of all the available evidence

Rather than a single disease, SOD represents a spectrum of malformative conditions involving different brain structures and characterised by a dynamic and sequential nature of endocrine dysfunction. Our large-scale data confirm recent views that ONH may represent just one component of the "SOD spectrum". Hypothalamic dysfunction might explain some of the shared phenotypes between ONH and SOD. Optic nerve and hypothalamo-pituitary abnormalities are the core features of the *erroneously* called "*Septo*-Optic Dysplasia" syndrome, whilst additional midline (corpus callosum) or hemispheric brain abnormalities may or not be present, with limited association with the endocrine phenotype of these patients. We propose that the condition should be renamed to reflect this evidence. The acronym "*HPOD" (Hypothalamo-Pituitary-Optic Dysplasia)*" may be a more appropriate term to describe the structural abnormalities associated with endocrine phenotypes in these patients.

followed at a single centre, and to compare their characteristics with children with Multiple Pituitary Hormone Deficiencies (MPHD) without any midline defects, and those with *isolated* ON Hypoplasia (ONH).

2. Methods

2.1. Patients

259 patients diagnosed with SOD (n = 171), MPHD (n = 53) or ONH (n = 35) between 1994 and 2015 at our tertiary/quaternary endocrine unit. Median follow-up duration was 8·00 years for SOD, 6·62 years for MPHD and 6·90 years for ONH (Table 1). SOD patients were divided into those with (SOD+) and those without (SOD-) hypopituitarism.

2.2. Study design

Retrospective longitudinal data collection. Clinical characteristics as well as mortality data were compared between SOD, MPHD and ONH cohorts. Endocrine morbidity was studied in SOD+ versus MPHD. Pituitary imaging findings were analysed in all groups and subgroups (SOD, MPHD, ONH, SOD+, SOD-) to evaluate associations between hypothalamo-pituitary (H-P), ON and midline brain abnormalities and clinical findings.

2.3. Ethic

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal written consent was not required.

2.4. Auxology

In addition to the standard definitions of obesity and leanness (Appendix, Materials and Methods), "extreme obesity" was defined as Body Mass Index (BMI) > 4 Standard Deviation Scores (SDS).

2.5. Endocrinology

GH, TSH, ACTH, gonadotrophin (Gn) deficiencies and Central Diabetes Insipidus (DI) were diagnosed according to current guidelines or recommendations (Appendix, Materials and Methods). Additionally, in children with low growth factors, poor growth velocity (GV), and structural H-P abnormalities, the overnight GH secretion was considered abnormal if less than 3 GH peaks >6·7 ng/L occurred over 12 h (samples obtained every 20 min) [16].

Assessment of the pituitary-gonadal axis was performed either during mini-puberty (known to be variable, for the purpose of this study: <18 months of age) or at the expected time for puberty (Appendix, Materials and Methods).

The degree of hypopituitarism was evaluated through the Endocrine Morbidity Score (EMS), adapted from DeVile et al and ranging from 1 (one deficit) to 5 (panhypopituitarism) [17].

2.6. Neuroimaging

Magnetic resonance images (MRI) were reviewed by one experienced neuroradiologist, and H-P, ON and midline brain abnormalities were reported.

2.7. Statistical analysis

BMI [18], GV [18] and Insulin-like Growth Factor 1 (IGF-1) [19] were expressed as SDS.

Table 1
Characteristics of children with septo-optic dysplasia (SOD), multiple pituitary hormone deficiencies (MPHD) and optic nerve hypoplasia (ONH).

	SOD (n:171)	MPHD (n:53)	ONH (n:35)	*p* value
M/F (%)	96/75 (56·1)	30/23 (56·6)	21/14 (60·0)	0·915
Age at SOD/MPHD/ONH diagnosis (years)	1·03 (1·92)	0·44 (3·37)	1·68 (1·86)	**0·004**
median (IQR) (range)	(0·01−14·92)	(0·01−11·02)	(0·19−8·50)	
Neonatal SOD, MPHD or ONH diagnosis n (%)	10/171 (5·8)	16/53 (30·2)	0 (0·0)	<**0·0001**
Follow-up duration (years)	8·00 (6·19)	6·62 (5·59)	6·90 (7·19)	0·494
median (IQR) (range)	(0·40−17·50)	(0·45−16·70)	(0·69-14·82)	
Age at last appointment (years)	9·24 ± 4·64	9·00 ± 4·66	9·54 ± 3·82	0·858
mean ± SD (range)	(0·52−21·00)	(0·46−21·48)	(1·03−15·01)	
Obesity at last appointment n (%)	51/161 (31·1)	21/51 (41·2)	4/33 (12·1)	**0·015**
Leanness at last appointment n (%)	9/161 (5·6)	0/53 (0·0)	2/33 (6·1)	0·175

n: number; M: males, F: females; IQR: Interquartile Range; SD: Standard deviation; SDS: SD Score.
p values <0·05 are highlighted in bold.
Age at last appointment was approximately normally distributed and comparison was made using one-way ANOVA.
Age at diagnosis and follow up durations were compared using Kruskal−Wallis.
Percentages were compared using Chi-square.

Anthropometric measures, age at diagnosis and last appointment, follow-up duration, and abnormalities in pubertal progress and body weight were compared between the SOD, MPHD and ONH cohorts using Kruskal−Wallis, ANOVA or chi-square, as appropriate. Where appropriate, the Bonferroni method is used to obtain an adjusted p-value cut-point to give overall 5% significance. This method assumes that measures tested are independent and hence highly conservative.

Differences in prevalence and age at onset of individual pituitary deficiencies were evaluated in SOD+ vs MPHD. Time to acquisition of each of the 5 deficits and to the first to occur were compared between diagnostic subgroups using Cox Proportional Hazards models. Differences according to demography and MRI findings were also evaluated. Interaction terms were added to the models to investigate differences in relationships with other factors between SOD+ and MPHD.

Differences in prevalence of deficits between groups were studied and Hazard ratios (HR) are presented with 95% confidence intervals (ci).

3. Results

3.1. Clinical characteristics, mortality and pubertal data in SOD vs MPHD vs ONH

3.1.1. General characteristics

Most SOD patients presented with the three diagnostic criteria of SOD (64·9%) and with ONH (89·9%) (87·4% bilateral, 12·6% unilateral).

MPHD was diagnosed earlier in life (median 0·44 vs 1·03 vs 1·68 years, for MPHD, SOD and ONH respectively, *p* = 0·004), and significantly more frequently in the neonatal period (Table 1).

The prevalence of obesity was significantly greater in MPHD than SOD and ONH, whilst leanness was documented exclusively in SOD and ONH, and "extreme obesity" in 3 SOD only (Table 1). In both SOD and MPHD, obesity was more frequent in subjects with DI, compared to those without DI [18/32 (56·3%) vs 53/180 (29·4%), diff (ci) 26·8% (8·5, 43·6%), *p* = 0·003].

3.1.2. Mortality

Mortality data were available from 144 SOD, 31 ONH and 50 MPHD. The mortality rate was 4·2% (6/144) in SOD (all of them had ONH) and 3·2% (1/31) in *isolated* ONH. No mortality was recorded in MPHD. In none of the deceased patients was the endocrine morbidity recorded as responsible for death, although one SOD patient had autonomic dysregulation suggestive of hypothalamic dysfunction. All deceased patients had complex phenotypes with cardiac, neurological, bone or respiratory involvement including one patient with cardiofaciocutaneous syndrome.

3.1.3. Minipuberty

More MPHD than SOD males were born with undervirilised external genitalia [70·0 vs 42·7%, diff (ci) 27·3% (6·8, 43·6%), *p* = 0·027] (Table 2A). Compared with SOD, MPHD with undervirilised genitalia had lower testosterone responses after 3 days and 3 weeks of HCG stimulation, and significantly lower LH and FSH responses after GnRH stimulation (Table 2A). Three SOD presented with isolated hypospadias, without biochemical features of Gn Deficiency (GnD).

3.1.4. Puberty

More MPHD than SOD were diagnosed with GnD [37·5% vs 15·8%, diff (ci) 21·7% (2·7, 42·5%), and significantly more received treatment for delayed or "slowly−progressing" puberty (Table 2B).

Central Precocious Puberty (CPP) or early/"rapidly-progressing" puberty were diagnosed in 7·0% SOD, 8·6% ONH and none of MPHD patients (Table 2B). 1 of 12 SOD with sexual precocity had otherwise preserved pituitary function (SOD-). Among SOD with sexual precocity, 11/12 SOD (91·7%) had a small anterior pituitary (SAP), 8/12 (66·7%) had Posterior Pituitary (PP) abnormalities (4 absence and 4 ectopia), 4/12 (27·3%) had pituitary stalk (PS) abnormalities (1 absence and 2 thinness), 1/12 (9·1%) had the Pituitary Stalk Interruption Syndrome (PSIS). 1/3 ONH with sexual precocity had SAP (33·3%).

Five out of 171 (2·9%) SOD and 2/35 (5·7%) ONH had isolated premature thelarche; 3/171 (1·7%) SOD had isolated premature menarche; 4/171 (2·3%) SOD and 3/35 (8·6%) ONH had isolated premature adrenarche. None of the MPHD had pubertal/adrenarche "variants".

3.2. Endocrine morbidity in SOD+ vs MPHD

Among SOD, only 39/171 (22·8%) had preserved pituitary function (SOD-) over up to 14·12 years of follow-up [median (IQR) 6·25 (3·41, 8·06) years]. Survival curves of times to each of the five pituitary deficits in the remaining SOD+ (n:132) vs MPHD (*n* = 53) are shown in Fig. 1. All pituitary deficits were more frequent and occurred significantly earlier in MPHD. DI occurred before 4 years of age in all (*n* = 5) MPHD, whilst 8/29 (27·6%) SOD+ were diagnosed with DI later (7·13 to 16·8 years) (Fig. 1).

We identified up to 70 patterns of evolution of 16 types of associations of pituitary deficits *(data not shown)*. The prevalence of different EMS in SOD+ vs MPHD is reported in Appendix, table 1. The most frequent combination was GH+TSH+ACTH, in both the SOD+ (30·7%) and MPHD (49·0%). DI never presented in isolation in SOD+, in contrast to the anterior pituitary deficits (21·6% for GH, 3·6% for TSH, 1·8% for ACTH and 0·9% for Gn).

Table 2A
Clinical and biochemical findings of likely GnRH Deficiency (GnD) and testicular dysfunction at minipuberty in males with septo-optic dysplasia (SOD) compared to those with multiple pituitary hormone deficiencies (MPHD).

Males	SOD (n:96)	MPHD (n:30)	p value
Undervirilised genitalia n (%)	41 (42·7)	21 (70·0)	**0·027**
Isolated micropenis	*7 (7·3)*	*6 (20·0)*	
Isolated hypospadias	*3 (3·1)*	*0 (0·0)*	
Isolated undescended testis/es	*13 (13·5)*	*4 (13·3)*	
2 of the previous features	*16 (16·7)*	*8 (30·0)*	
3 of the previous features	*2 (2·1)*	*3 (26·7)*	
Males with undervirilised genitalia	SOD (n:41)	MPHD (n:21)	p value
Age at GnRH test (years) median (IQR) (range)	0·62 (0·91) (0·18−1·50) (n:16)	0·17 (0·09) (0·02−0·21) (n:8)	**<0·0001**
Peak LH response to GnRH test (IU/L) median (IQR) (range)	5·35 (9·45) (0·20−27·90) (n:16)	0·10 (0·15) (0·05−0·30) (n:8)	**<0·0001**
Peak FSH response to GnRH test (IU/L) median (IQR) (range)	3·00 (6·65) (0·20−16·50) (n:16)	0·10 (0·00) (0·05−0·20) (n:8)	**<0·0001**
LH peak < 5 IU/L to GnRH test n (%)	8/16 (50·0)	8/8 (100·0)	0·0500
Undetectable LH to GnRH test n (%)	1/15 (6·6)	5/7 (71·4)	**0·0015**
Age HCG test (years) median (IQR) (range)	0·88 (0·90) (0·18−1·68) (n:16)	0·18 (0·38) (0·01-1·63) (n:12)	0·007
Peak Testosterone to 3 day HCG test (nmol/L) median (IQR) (range)	9·74 (12·77) (0·35−21·50) (n:16)	2·67 (1·45) (0·35−6·03) (n:12)	0·011
Insufficient (< 3·6 nmol/L) 3 day Testosterone response to HCG stimulation n (%)	3/14 (21·4)	8/10 (80·0)	0·011
Peak Testosterone to 3 week HCG test (nmol/L) median (IQR) (range)	19·90 (20·10) (2·91−32·50) (n:9)	8·22 (4·33) (3·44−13·00) (n:11)	0·052
Insufficient (<9·5 nmol/L) 3 day Testosterone response to HCG stimulation n (%)	3/9 (33·3)	8/11 (72·7)	0·078

IQR: Interquartile range, HCG: human chorionic gonadotropin.
Bonferroni adjusted p-value of 0.005 identifies differences between the SOD and MPHD cohorts within the under-virilised genitalia subgroup that are significant at the 5% level. These are highlighted in bold.
Continuous data were compared using Mann−Whitney test.
Percentages were compared using Chi-square.
Note that the *n* in the "males with undervirilised genitalia" reflect the patients tested only (GnRH and hCG test).

The majority of patients with hypopituitarism had GHD with the exception of 11 (8·3%) SOD+ and 2 (3·8%) MPHD. 10/11 SOD+ with normal GH secretion were > 1 year old (range 1·49-15·46 years). Four of them had multiple pituitary deficits (2 TSH+ACTH+DI, 1 TSH +ACTH, 1 TSH+DI) whilst the remaining had isolated deficiencies (4 TSH, 2 ACTH, 1 Gn). The two MPHD without GHD (1 TSH+ACTH, 1 TSH+ACTH+DI) were < 1 year old at last appointment (0·57 and 0·62 years), and will likely go on and develop GHD.

As many of our patients had not attained pubertal age, the next section will not consider Gn deficiency.

As shown in Fig. 2, 90% of the SOD+ had the first deficiency by 8·54 years, compared to 4·80 years for the MPHD. The time to first pituitary deficiency was significantly associated with the EMS [HR 1·59 (1·36, 1·85) higher for each additional deficit subsequently seen (Appendix, Fig. 1)]. The pattern was similar for SOD+ and MPHD (interaction p=0·896).

There were no significant differences in the biochemical diagnostic features of GH, TSH and ACTH deficiencies in SOD+ vs MPHD (Appendix, Table 2).

Five SOD+ (but none of the MPHD) had neurosecretory GH dysfunction (age at diagnosis 2·55-14·64 years). All had SAP, 2 had

Posterior Pituitary Absence (PPA) and 1 had PSIS [SAP + Ectopic Posterior Pituitary (EPP) + Pituitary Stalk Absence (PSA)].

10/78 SOD+ (13·8%) and 4/45 MPHD (8·9%) exhibited raised (>6 mU/L) TSH concentrations (up to 9·8 mU/L in SOD and 16·1 mU/L in MPHD) and were diagnosed with TSHD after exclusion of primary hypothyroidism.

3.3. Pituitary imaging in all groups and subgroups

A significantly higher prevalence of severe H-P abnormalities, mainly EPP [80·0 vs 41·6%, diff (ci) 38·4, (22·7, 50·4%)], and PSIS [46·9 vs 29·5%, diff (ci) 17·4% (1·6, 33·0%)] was documented in MPHD compared to SOD+. Rare abnormalities such as AP and PP enlargement or PS thickening were documented in the SOD+ group only (Table 3).

Half of patients with *isolated* ONH and 73·0% of the SOD- had SAP but preserved pituitary function at 10·22 (5·96, 12·98) years (range 1·65-14·82) and 6·20 (3·38, 8·00) years (range 0·50-12·09) of follow-up, respectively.

Among DI patients, 17/26 (65·4%) SOD and 1/5 (20·0%) MPHD had PP Absence (PPA), 6/26 (23·1%) SOD and 3/5 (60·0%) MPHD had a normal PP, and 3/26 (11·5%) SOD and 1/5 (20·0%) MPHD had EPP. Among patients without DI, 18/128 (14·1%) SOD and 2/45 (4·4%) MPHD had PPA.

Patients with PPA and EPP were more likely to develop their first deficiency earlier (Appendix, Table 3A). The following MRI findings were significantly associated with an earlier onset of specific deficits: (i) PPA with all except GnD; (ii) EPP and PSIS with all AP deficits, whilst they were protective for DI; (iii) PSA with GHD, TSHD and ACTHD (Appendix, Table 3B).

Further investigations revealed that patterns of SOD+ time to first deficit and to development of GH/TSH/ACTH deficiencies were more similar to MPHD amongst those with PSIS, PSA and PP abnormalities (Figs. 3−5). In particular, there were significant interactions between PSA and diagnosis; SOD+ with PSA were similar to MPHD in terms of time to first deficiency, and to GH/TSH/ACTH deficiencies (Fig. 3, all p-values < 0·03). For PP abnormalities, the patterns were similar (Fig. 4), despite only attaining statistical significance for time to first deficit (p = 0·045) and being borderline for time to GHD (p = 0·0585). Similarly, for PSIS, Fig. 5 shows that SOD+ with PSIS had deficiencies at times comparable to MPHD, despite the interactions not being statistically significant, probably due to small numbers within subgroups (p-values ranged from 0·0686 for ACTHD to 0·25 for time to first deficit).

There were insufficient data to investigate the interactions for GnD, as this was not diagnosed until puberty, and for DI, which was uncommon in MPHD.

There was no clear evidence of association between ONH (bilateral vs unilateral) and midline brain abnormalities, and time to any pituitary deficiencies, although estimates are imprecise and some confidence intervals are very wide (Appendix, Tables 3A and 3B).

3.4. Molecular diagnoses

In this cohort, genetic testing was performed in 144/171 (84.2%) patients with SOD and 50/53 (94%) patients with MPHD. Amongst these, genetic variants were identified in 6/144 (4.2%) SOD and 3/50 (6.0%) MPHD. These included *PROKR2* (n:5) and *SOX2* (n:1) for SOD and *PROKR2* (n:1), *LHX4* (n:1), and *GLI2* (n:1) for MPHD. More details about the genotype/phenotype correlation and the detection rates for genetic mutations in these cohorts have been previously published by our centre and they are beyond the scope of this study.

4. Discussion

To our knowledge, this is the largest single-centre follow up study on the endocrine morbidity and mortality of children with SOD and related disorders.

Table 2B
Puberty in children with septo-optic sysplasia (SOD), multiple pituitary hormone deficiencies. (MPHD) and optic nerve hypoplasia (ONH).

	SOD (n:171)	MPHD (n:53)	ONH (n:35)	*p* value	Percentage difference	Confidence interval
Spontaneous puberty achieved at the expected ages (8-12y F, 9-13y M)	54/66 (81·8)	7/15 (46·7)	13/14 (92·8)	**0·004**	36·7*	11·1, 59·6*
n (%) (M, F)	(27M, 27F)	(5M, 2F)	(7M, 6F)		-9·5°	−21·8, 15·8°
					46·2#	12·6, 26·6#
Likely GnD (based on clinical and biochemical findings)	12/76 (15·8)	9/24 (37·5)	NA	0·023	21·7	2·7, 42·5
n (%) (M, F)	(4M, 8F)	(6M, 3F)				
Treatment for delayed/slowly-progressing puberty	9/95 (9·5)	9/28 (32·1)	NA	**0·003**	22·7	6·6, 41·7
n (%) (M, F)	6 DP (2M, 4F)	7 DP (4M, 3F)				
	3 SPP (2M, 1F)	2 SPP (2M)				
Treatment for precocious or early/rapidly-progressing puberty	12/171 (7·0)	0/53	3/35 (8·6)	0·078	7·0*	-0·4, 11·9*
n (%) (M, F)	4 CPP (2M, 2F)		0 CPP		-1·6°	-15·7, 5·9°
	8 EP/RPP (5M, 3F)		3 EP/RPP (2 M, 1F)		-8·6#	-22·4, 0·2#

y: years; M: male, F: female, NA: Not Applicable; GnD: GnRH Deficiency; CPP: Central Precocious Puberty; EP: Early puberty; RPP: Rapidly-progressing puberty; DP: Delayed puberty, SPP: Slowly-progressing puberty.
Bonferroni adjusted *p*-value of 0.0125 is used to identify differences between SOD, MPHD and ONH that are significant at the 5% level. These are highlighted in bold.
Percentages were compared using Chi-square.
* *SODvsMPHD.*
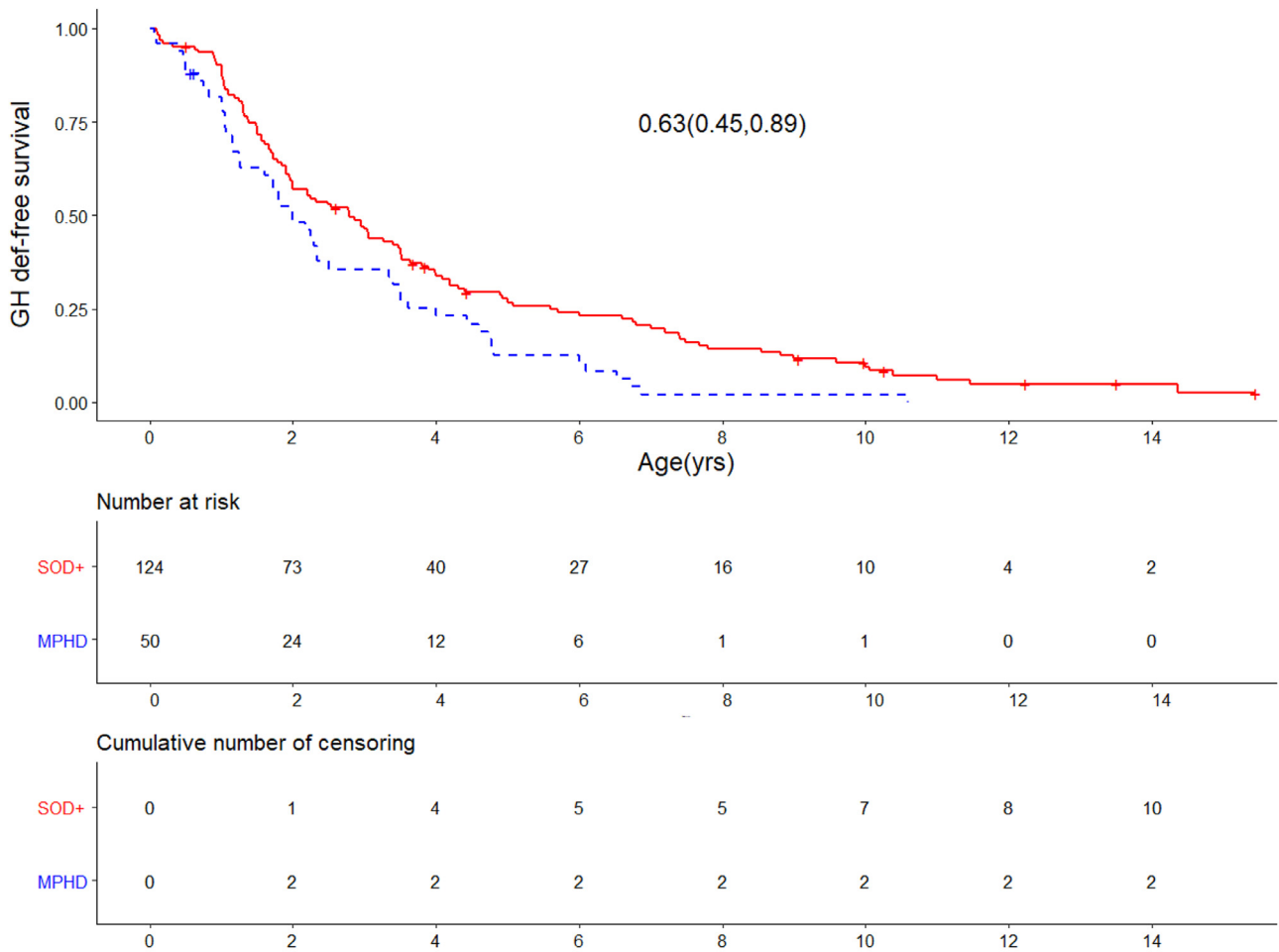° *SODvsONH.*
\# *MPHDvsONH.*

Fig. 1. Survival curves of time to each pituitary deficiency in SOD+ compared to MPHD Hazard ratio (95% CI). The diagrams show that all anterior (GH, TSH, ACTH, Gn deficiencies) pituitary deficits occur significantly earlier in MPHD than SOD+. Diabetes insipidus occurred later on average for the MPHD patients but the difference was not significant. Def: deficiency; SOD +: Septo-Optic Dysplasia with pituitary deficits; MPHD: Multiple Pituitary Hormone Deficiency; GH: Growth Hormone, TSH: Thyroid-Stimulating Hormone; ACTH: AdrenoCorticoTropic Hormone; Gn: Gonadotrophin; CI: confidence interval; yrs: years.

Comparison between subgroups revealed three main endocrine phenotypes: (1) *MPHD:* higher occurrence and earlier onset of AP deficits and higher prevalence of severe structural H-P abnormalities; I2) *SOD+:* wider range of age at presentation of deficits and of body weight and pubertal disorders, heterogeneous H-P structural abnormalities, higher prevalence of DI; (3) *ONH/SOD-:* preserved pituitary function but at risk of hypopituitarism (presence of SAP), possible CPP, obesity/leanness.
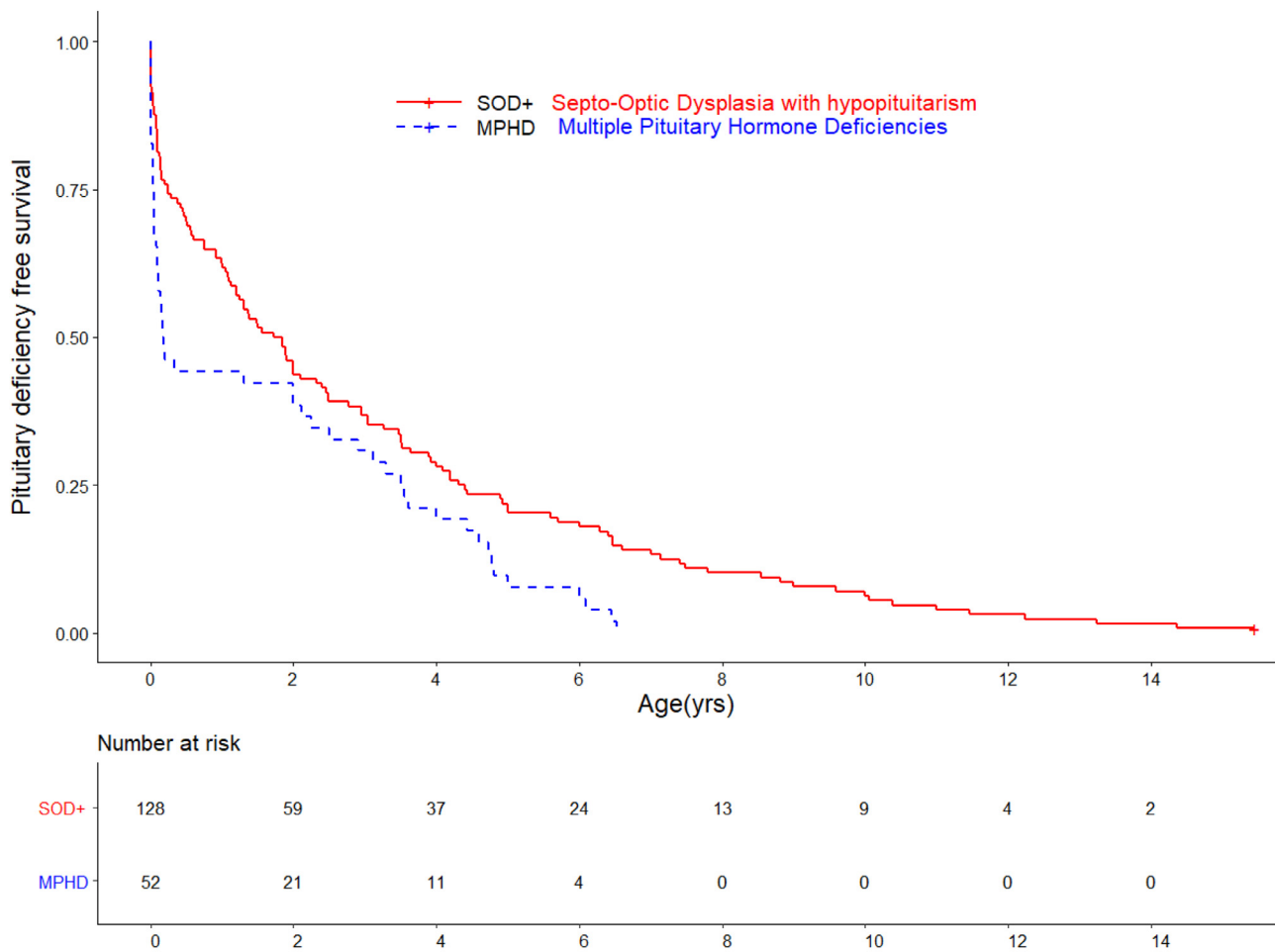
Fig. 2. Survival curves of time to first pituitary deficiency in SOD+ compared to MPHD.The diagram shows that the first pituitary deficit occurs significantly earlier in MPHD than SOD+. Median age (CI) in years of first pituitary deficiency: 1.78 (1.2, 2.5) in SOD+ and 0.18 (0.1, 2.5) in MPHD; HR 0.62 (0.44, 0.86). There were no censored observations for this variable. SOD +: Septo-Optic Dysplasia with pituitary deficits; MPHD: Multiple Pituitary Hormone Deficiency; CI: Confidence Interval; HR: Hazard Ratio; yrs: years.

Table 3

Comparison between the structural hypothalamo-pituitary abnormalities of the following 5 groups: Septo-optic dysplasia (SOD), multiple pituitary hormone deficiencies (MPHD), optic nerve hypoplasia (ONH), SOD with pituitary deficits (SOD+), SOD without pituitary deficits (SOD−).

	SOD (n:171)	MPHD* (n:53)	ONH (35)	SOD+* (n:132)	SOD- (n:39)	p value*	Percentage* difference	Confidence* interval
AP abnormalities n (%)	135/162 (83·3)	49/50 (98·0)	17/34 (50·0)	108/125 (86·4)	27/37 (73·0)	0·127	11·6	-1·8, 18·9
AP Absence	2/162 (1·2)	1/50 (2·0)	0/34 (0·0)	2/125 (1·6)	0/37 (0·0)			
Small AP (SAP)	132/162 (81·5)	48/50 (96·0)	17/34 (50·0)	105/125 (84·0)	27/37 (73·0)			
AP Enlargement	1/162 (0·6)	0/50 (0·0)	0/34 (0·0)	1/125 (0·8)	0/37 (0·0)			
PP abnormalities n (%)	96/161 (59·3)	43/50 (86·0)	0/34 (0·0)	84/125 (67·2)	12/37 (29·6)	<0·0001	18·8	4·4, 29·9
PP Absence (PPA)	34/162 (21·0)	3/50 (6·0)	0/34 (0·0)	27/125 (21·6)	7/37 (18·9)			
PP Hypoplasia	8/162 (4·9)	0/50 (0·0)	0/34 (0·0)	4/125 (3·2)	4/37 (10·8)			
PP Enlargement	1/162 (0·6)	0/50 (0·0)	0/34 (0·0)	1/125 (0·8)	0/37 (0·0)			
Ectopic PP (EPP)	53/162 (32·7)	40/50 (80·0)	0/34 (0·0)	52/125 (41·6)	1/37 (2·7)			
PS abnormalities n (%)	78/157 (49·7)	23/49 (46·9)	0/34 (0·0)	67/122 (54·9)	11/35 (31·4)	0·629	*8·0*	-8·3, 23·7
PS Absence (PSA)	32/157 (20·4)	11/49 (25·4)	0/34 (0·0)	30/122 (24·6)	2/35 (5·7)			
Thin PS	43/157 (27·4)	10/49 (10·4)	0/34 (0·0)	34/122 (27·9)	9/35 (25·7)			
Interrupted PS	2/157 (1·3)	2/49 (4·1)	0/34 (0·0)	2/122 (1·6)	0 (0·0)			
Thick PS	1/157 (0·6)	0/49 (0·0)	0/34 (0·0)	1/122 (0·8)	0 (0·0)			
Pituitary Stalk Interruption Syndrome (PSIS) n (%)	37/159 (23·3)	23/49 (46·9)	0/34 (0·0)	36/122 (29·5)	1/37 (2·7)	**0·030**	17·4	1·6, 33·0

AP: Anterior pituitary; PP: Posterior pituitary; PS: Pituitary Stalk; PSIS: SAP + EPP + Absent/Thin/Interrupted Stalk.

p values < 0·05 are highlighted in bold.

Percentages were compared using Chi-square.

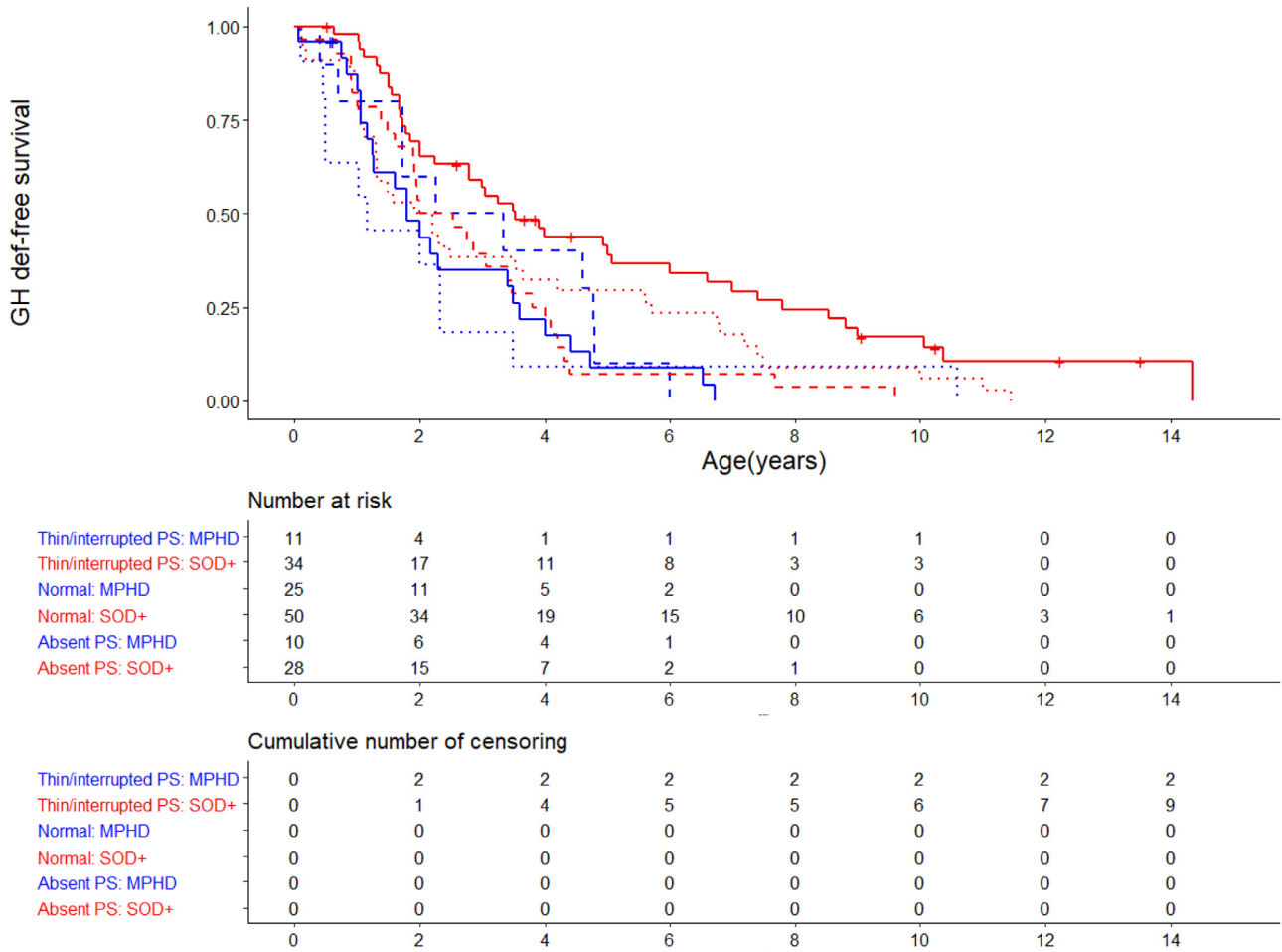* *p* values, percentage differences and confidence intervals for SOD+ vs MPHD.

Fig. 3. Interactions between Pituitary Stalk (PS) abnormalities and SOD+ or MPHD diagnosis in relation to time to GH, TSH, ACTH deficiencies and first pituitary deficit. The diagrams show that patterns of SOD+ time to first pituitary deficit and to development of GH/TSH/ACTH deficiencies are more similar to MPHD amongst those with PSA abnormalities (Absent and Thin/Interrupted PS) (all p-values < 0·03). Def: Deficiency; PSA: Pituitary Stalk Abnormalities; SOD +: Septo-Optic Dysplasia with pituitary deficits; MPHD: Multiple Pituitary Hormone Deficiency; GH: Growth Hormone, TSH: Thyroid-Stimulating Hormone; ACTH: AdrenoCorticoTropic Hormone, yrs: years.

Although MPHD exhibit an earlier onset of deficits, we have identified a subgroup of SOD+ with specific MRI abnormalities (PS/PP and PSIS) at risk of developing deficiencies earlier, making their endocrine phenotype more similar to those with MPHD. In both SOD+ and MPHD, an earlier onset predicted a more severe phenotype with a higher number of deficits. Such association has previously been documented in patients with PSIS [20].

Asynchronous evolution of deficits has been extensively described in children with and without midline brain abnormalities [21]. We were unable to identify specific patterns of evolution characteristic of SOD+ or MPHD, indicating the importance of life-long careful monitoring in all patients. Indeed, SOD+ continued to develop deficits throughout adolescence (up to 14 years for the first deficit, 17 years for DI and 16 years for ACTHD). To our knowledge, this is the first study documenting "late onset" DI in children with SOD. Interestingly, in our cohort, DI presented only in combination with AP deficits, suggesting that isolated DI should raise the suspicion of alternative diagnoses such as acquired hypothalamic/PP dysfunction or genetic causes. Most studies reported the development of additional deficits in children presenting with isolated GHD [8,22], whilst in our cohort, a small number of SOD and MPHD had preserved GH reserve. This finding challenges previous assumptions that the first deficit to occur in children with hypopituitarism is always GHD, or that GH is invariably deficient in these patients [8,22].

When interpreting our data about prevalence/evolution of deficits, it must be pointed out that in our cohort: i) the majority of patients were pre-pubertal and thus the prevalence of some pituitary deficits (particularly GnD) might be underestimated, ii) SOD had a higher prevalence of "classic triad" (65%) and hypopituitarism (77%) compared to previous studies (24−30% [6,23] and 50−66% [6,7,12,23], respectively), suggesting a possible selection bias of more severe phenotypes referred to our centre.

We have documented unusual biochemical findings associated with GH and TSH deficiency. Five SOD patients who had a normal GH response to dynamic stimulation showed an abnormal overnight pattern of GH secretion, suggesting a more complex combined hypothalamo (GHRH-somatostatin)-pituitary(somatotrope) axis disruption, compared to MPHD. Although central hypothyroidism is classically diagnosed by low FT4 concentrations and inappropriately low/normal TSH, in our cohort a significant number of patients had mild-moderately raised TSH concentrations. The mechanism underlying the TSH elevation remains unexplained, but hypothalamic dysfunction, or the secretion of biologically inactive TSH, have been suggested [24].

We identified striking differences in the range of pubertal disorders between MPHD vs SOD/ONH. SOD can present with the whole spectrum ranging from delayed to precocious puberty, whilst MPHD generally only develop GnD, with a higher prevalence of undervirilised genitalia and testicular dysfunction. In our cohort, GnD was not associated with isolated hypospadias. This is in agreement with the recent European Consensus Statement on congenital GnD stating that, in contrast to cryptorchidism and micropenis, hypospadias results from an early foetal developmental defect, before the initiation of endogenous
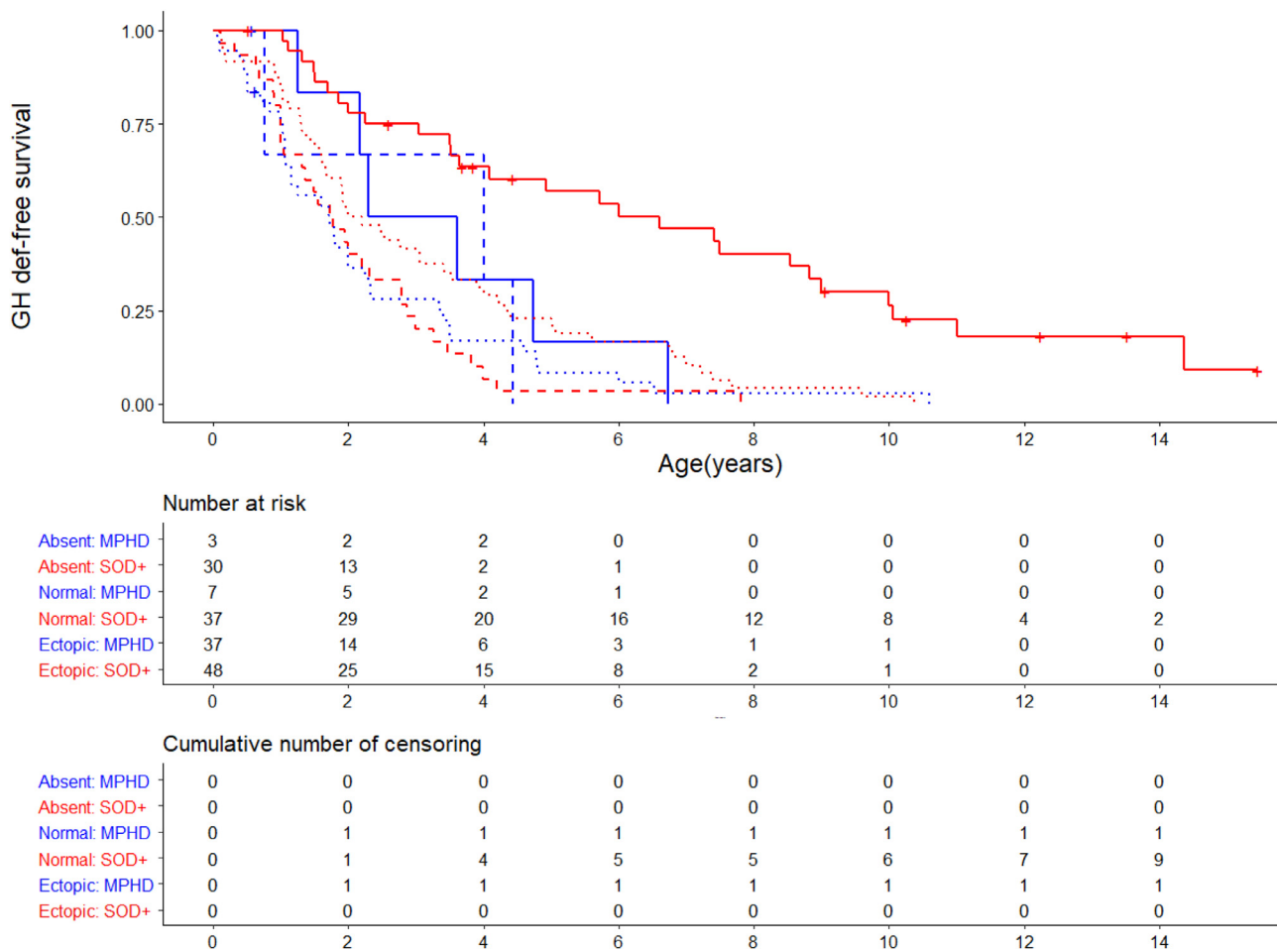
Fig. 4. Interactions between Posterior Pituitary (PP) abnormalities and SOD+ or MPHD diagnosis in relation to time to GH, TSH, ACTH deficiencies and first pituitary deficit. The diagrams show that patterns of SOD+ time to first pituitary deficit and to development of GH/TSH/ACTH deficiencies are more similar to MPHD amongst those with PP abnormalities (Absent and Ectopic PP). Def: Deficiency; PP: Posterior Pituitary; SOD +: Septo-Optic Dysplasia with pituitary deficits; MPHD: Multiple Pituitary Hormone Deficiency; GH: Growth Hormone, TSH: Thyroid-Stimulating Hormone; ACTH: AdrenoCorticoTropic Hormone, yrs: years.

GnRH activity [25]. Interestingly, in our cohort, a number of SOD and ONH patients, but no MPHD, had CPP or pubertal/adrenarche "variants". These data are consistent with previous reports from smaller SOD case series [9,10,26,27], whilst a similar tendency has never been described before in *isolated* ONH. The midline brain developmental insult in SOD likely starts between the 5th and 8th gestational weeks [28]. Arrival of GnRH neurons in the hypothalamus later (by week 13th) might explain how GnRH secretion can be retained. Moreover, abnormal H-P anatomy may alter the normal suppression of GnRH neurons from higher brain centres, leading to earlier onset of gonadotrophin secretion [26]. The presence of two extreme forms of abnormal pubertal development in the same condition might be explained by the presence of lesions in different hypothalamic regions, with autopsy studies showing that lesions in the posterior hypothalamus are associated with sexual precocity, whereas lesions of the anterior hypothalamus are associated with hypogonadism [29]. In our SOD cohort, no patients evolved from precocious to delayed/absent puberty, in contrast to what has been reported in children with diencephalic and hypothalamic dysfunction due to optic gliomas [30]. However, not all patients with CPP were post-pubertal at the last appointment, hence some may still develop GnD later in life. Of note, the neuroimaging features of patients presenting with sexual precocity were not different from the wider SOD/ONH groups showing that this clinical presentation might be an expression of hypothalamic dysfunction which is difficult to capture with conventional MRI techniques.

Variable hypothalamic dysfunction could also partially explain the distinct body weight disorders between the three groups, with SOD/ONH again showing the most heterogeneous phenotypes ranging from leanness to extreme obesity. Leanness has been previously documented in patients with optic gliomas, likely associated with hypothalamic pathology [30]. Although most patients with SOD had ONH, interestingly all SOD with sexual precocity and with leanness and extreme obesity had *bilateral* ONH, whilst these pubertal and body weight disorders were not reported in the few SOD patients with normal eye development.

In the light of the above observations, we could hypothesise that children with *isolated* ONH may have some degree of hypothalamic dysfunction, and that they form just one end of the SOD spectrum, as also supported by previous data [3]. It must be noted that, in our cohort, half of the patients with *isolated* ONH had a SAP, and they may still develop pituitary deficits later in life to fulfill the criteria for SOD. Hence the boundaries between these two categories are rather blurred.

Data on neuroimaging abnormalities matched the distinctive endocrine phenotypes across groups.

EPP or PSIS have been associated with hypopituitarism in different groups of at-risk patients, including ONH [8,11,31]. In our study, EPP and PS abnormalities were associated with an earlier onset of AP deficits in both SOD+ and MPHD. Importantly, they were more prevalent in MPHD than SOD+ and virtually absent in SOD- and *isolated* ONH. They also allowed identification of a subgroup of SOD+ at higher risk
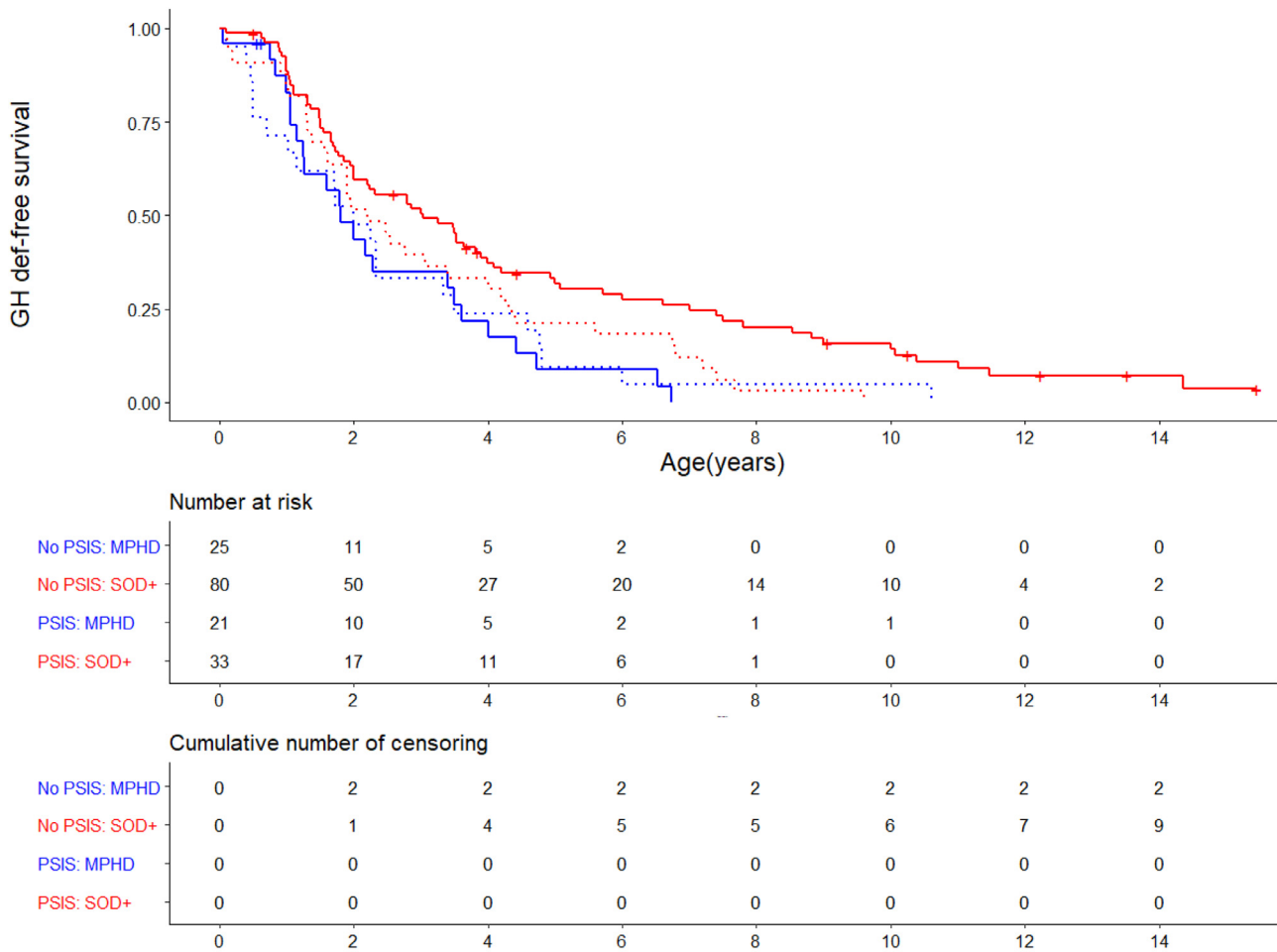
Fig. 5. Interactions between Pituitary Stalk Interruption Syndrome (PSIS) and SOD+ or MPHD diagnosis in relation to time to GH, TSH, ACTH deficiencies and first pituitary deficit. PSIS is defined by the following abnormalities: Small Anterior Pituitary + Ectopic Posterior Pituitary + Pituitary Stalk Absence. The diagrams show that patterns of SOD+ time to first pituitary deficit and to development of GH/TSH/ACTH deficiencies are more similar to MPHD amongst those with PSIS (p-values ranged from 0·0686 for ACTH Deficiency to 0·25 for time to first deficit). PSIS: Pituitary Stalk Interruption Syndrome; SOD +: Septo-Optic Dysplasia with pituitary deficits; MPHD: Multiple Pituitary Hormone Deficiency; GH: Growth Hormone, TSH: Thyroid-Stimulating Hormone; ACTH: AdrenoCorticoTropic Hormone, yrs: years.

of earlier onset AP deficits. Hence, overall, they allowed differentiation between patients with preserved and abnormal pituitary function and, in those with hypopituitarism, they correlated with the timing of onset of deficits.

In contrast, PPA and SAP seemed to have a lower utility in distinguishing those children who will develop DI or AP deficits, respectively. Among patients with DI, 23% had a normal PP, confirming previous data suggesting low predictive value of PP abnormalities for development of DI [11]. Interestingly, in our cohort, PPA were equally associated with the development of posterior and *anterior* pituitary deficits. Although an EPP usually points to an evolving anterior pituitary dysfunction [32], we have also documented early onset DI (0·05 to 1·38 years for SOD and 3·8 years for MPHD) in three SOD and one MPHD with EPP. These data are in agreement with a previous study demonstrating that patients with EPP may have a defect in the osmoreceptors regulating AVP secretion [13]. In our cohort most, but not all, patients with hypopituitarism had SAP. SAP has been reported in 74-100% of patients with hypopituitarism [33]. This variability could be related to the relative lack of convincing age-related objective size criteria for the AP.

Despite the association in our study between some H-P abnormalities and specific pituitary deficits, given the possible appearance of deficiencies up to late adolescence (particularly for GnD) and the relative low incidence of some of them (e.g. DI), disentangling the relationship between MRI abnormalities and specific endocrinopathies is challenging.

We could not find any association between the presence of septum pellucidum and corpus callosum abnormalities and the age at onset of deficits. This observation reinforces recent views that abnormalities in midline brain structures may not be linked with hypopituitarism [3]. Despite the relatively frequent occurrence of abnormalities in the corpus callosum in patients with ONH, they correlate more with the neurobehavioral features in these patients [34], whilst septum pellucidum abnormalities might even be incidental as they do not correlate with vision status, nor with endocrinopathies, or developmental outcomes [3]. In contrast, the onset of pituitary deficits has been extensively associated with ONH, regardless of its laterality [3,31,35]. A severe visual phenotype with blindness has been recently reported as a risk factor for hypopituitarism in a large cohort of patients with ONH [31], more than the presence of *bilateral (vs unilateral)* ONH, as also confirmed in our study. It could be hypothesised that the presence of abnormal connectivity between the optic nerves and hypothalamus/other brain structures might in part explain the complexity and heterogeneity in the presenting features of SOD/ONH children. However, given the poor resolution of conventional MRI techniques to anatomically characterise the hypothalamus, this hypothesis remains speculative.

Excess mortality has been previously documented in patients with hypopituitarism secondary to brain tumours [36]. This is the first study providing mortality data in patients with congenital hypopituitarism and midline brain/ON maldevelopment. In our cohort, premature

death in childhood occurred exclusively in patients with ONH associated with complex phenotypes and never in patients with isolated MPHD, suggesting that hypopituitarism may just be a contributory factor for death in these patients, whilst the presence of other brain/optic nerve abnormalities seems to be more frequently associated with complex phenotypes leading to death. It must be pointed out that, in our cohort, it is most likely that all patients were properly replaced with hormones and patient compliance to therapy was good. A recent met-analysis in adults with hypopituitarism due to various aetiologies has shown that hypopituitarism tends to increase premature mortality in affected individuals, and that GH replacement seems to improve the overall mortality [37]. However, the role of other pituitary replacement therapies was not discussed in that study, which was also potentially biased by the use of post-marketing data.

The strengths of our study are: (i) long-term longitudinal characterisation of the endocrine morbidity of patients with SOD, MPHD and ONH recruited from a large single-centre cohort; (ii) efforts to characterise patients with midline defects, hypopituitarism and ON abnormalities as part of a wider spectrum of disease, and (iii) extensive description of the evolution of pituitary deficits and the pubertal phenotypes over time. The limitations are: (i) retrospective nature of the study and (ii) childhood (vs adulthood) cohort: some deficiencies might develop in adulthood due to the evolving nature of these conditions.

Rather than a single disease entity, SOD represents a spectrum of malformative conditions involving different brain structures and characterised by a dynamic and sequential nature of endocrine dysfunction. In contrast to SOD, MPHD tends to display a relatively more homogeneous phenotype of (mainly) early AP failure. It can be speculated that varying insults at different stages of embryonic development affecting H-P and ON development are responsible for the wide spectrum of endocrine morbidities observed in the SOD population.

Specific MRI abnormalities predispose to a higher risk of early onset pituitary deficiencies, placing some SOD+ at a similar risk compared to MPHD. However, neuroimaging findings can predict the evolution of endocrine deficits only to some extent, hence lifelong regular surveillance is essential in all groups to enable prompt diagnosis of evolving endocrinopathies.

Our large-scale data confirm recent views that ONH may represent just one component of the "SOD spectrum". Hypothalamic dysfunction might explain some of the shared phenotypes between ONH and SOD. ON and H-P abnormalities are the core features of the erroneously called "Septo-Optic Dysplasia" syndrome, whilst additional midline (corpus callosum) or hemispheric brain abnormalities may or not be present, with limited association with the endocrine phenotype of these patients. The relationship between corpus callosum and/or hemispheric brain abnormalities and the neurobehavioral phenotypes of these patients deserves further study.

We suggest that the condition should be renamed to reflect this evidence. The acronym "HPOD" (Hypothalamo-Pituitary-Optic Dysplasia) may be a more appropriate term to describe the various brain structures predicting endocrine phenotypes in these patients.

Declaration of Competing Interest

The authors have nothing to declare.

Acknowledgments

Funding

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2019.11.017.

References

[1] Patel L, McNally RJ, Harrison E, Lloyd IC, Clayton PE. Geographical distribution of optic nerve hypoplasia and septo-optic dysplasia in Northwest England. J Pediatr 2006;148(1):85–8.

[2] Garne E, Rissmann A, Addor MC, Barisic I, Bergman J, Braz P, et al. Epidemiology of septo-optic dysplasia with focus on prevalence and maternal age - A EUROCAT study. Eur J Med Genet 2018;61(9):483–8.

[3] Garcia-Filion P, Borchert M. Optic nerve hypoplasia syndrome: a review of the epidemiology and clinical associations. Curr Treat Options Neurol 2013;15(1):78–89.

[4] Kelberman D, Dattani MT. Genetics of septo-optic dysplasia. Pituitary 2007;10 (4):393–407.

[5] Fang Q, George AS, Brinkmeier ML, Mortensen AH, Gergics P, Cheung LY, et al. Genetics of combined pituitary hormone deficiency: roadmap into the genome era. Endocr Rev 2016;37(6):636–75.

[6] Atapattu N, Ainsworth J, Willshaw H, Parulekar M, MacPherson L, Miller C, et al. Septo-optic dysplasia: antenatal risk factors and clinical features in a regional study. Horm Res Paediatr 2012;78(2):81–7.

[7] Birkebaek NH, Patel L, Wright NB, Grigg JR, Sinha S, Hall CM, et al. Endocrine status in patients with optic nerve hypoplasia: relationship to midline central nervous system abnormalities and appearance of the hypothalamic-pituitary axis on magnetic resonance imaging. J Clin Endocrinol Metab 2003;88(11):5281–6.

[8] Deal C, Hasselmann C, Pfäffle RW, Zimmermann AG, Quigley CA, Child CJ, et al. Associations between pituitary imaging abnormalities and clinical and biochemical phenotypes in children with congenital growth hormone deficiency: data from an international observational study. Horm Res Paediatr 2013;79(5):283–92.

[9] Freude S, Frisch H, Wimberger D, Schoeber E, Hüsler G, Waldhauser F, et al. Septo-optic dysplasia and growth hormone deficiency: accelerated pubertal maturation during GH therapy. Acta Paediatr. 1992;81(8):641–5.

[10] Huseman CA, Kelch RP, Hopwood NJ, Zipf WB. Sexual precocity in association with septo-optic dysplasia and hypothalamic hypopituitarism. J Pediatr 1978;92 (5):748–53.

[11] Mehta A, Hindmarsh PC, Mehta H, Turton JP, Russell-Eggitt I, Taylor D, et al. Congenital hypopituitarism: clinical, molecular and neuroradiological correlates. Clin Endocrinol 2009;71(3):376–82.

[12] Riedl S, Vosahlo J, Battelino T, Stirn-Kranjc B, Brugger PC, Prayer D, et al. Refining clinical phenotypes in septo-optic dysplasia based on MRI findings. Eur J Pediatr 2008;167(11):1269–76.

[13] Secco A, Allegri AE, di Iorgi N, Napoli F, Calcagno A, Bertelli E, et al. Posterior pituitary (PP) evaluation in patients with anterior pituitary defect associated with ectopic PP and septo-optic dysplasia. Eur J Endocrinol 2011;165(3):411–20.

[14] Vedin AM, Karlsson H, Fink C, Borchert M, Geffner ME. Presenting features and long-term effects of growth hormone treatment of children with optic nerve hypoplasia/septo-optic dysplasia. Int J Pediatr Endocrinol 2011;2011(1):17.

[15] Webb EA, Dattani MT. Septo-optic dysplasia. Eur J Hum Genet. 2010;18(4):393–7.

[16] Spiliotis BE, August GP, Hung W, Sonis W, Mendelson W, Bercu BB. Growth hormone neurosecretory dysfunction. A treatable cause of short stature. JAMA 1984;251(17):2223–30.

[17] DeVile CJ, Grant DB, Hayward RD, Stanhope R. Growth and endocrine sequelae of craniopharyngioma. Arch Dis Child 1996;75(2):108–14.

[18] Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. Arch Dis Child 1995;73(1):17–24.

[19] Bedogni G, Giannone G, Maghnie M, Giacomozzi C, Di Iorgi N, Pedicelli S, et al. Serum insulin-like growth factor-I (IGF-I) reference ranges for chemiluminescence assay in childhood and adolescence. Data from a population of in- and outpatients. Growth Horm IGF Res 2012;22(3-4):134–8.

[20] Bar C, Zadro C, Diene G, Oliver I, Pienkowski C, Jouret B, et al. Pituitary stalk interruption syndrome from infancy to adulthood: clinical, hormonal, and radiological assessment according to the initial presentation. PloS One 2015;10(11):e0142354.

[21] Traggiai C, Stanhope R. Endocrinopathies associated with midline cerebral and cranial malformations. J Pediatr 2002;140(2):252–5.

[22] Blum WF, Deal C, Zimmermann AG, Shavrikova EP, Child CJ, Quigley CA, et al. Development of additional pituitary hormone deficiencies in pediatric patients originally diagnosed with idiopathic isolated GH deficiency. Eur J Endocrinol 2013;170(1):13–21.

[23] Morishima A, Aranoff GS. Syndrome of septo-optic-pituitary dysplasia: the clinical spectrum. Brain Dev 1986;8(3):233–9.

[24] Persani L, Brabant G, Dattani M, Bonomi M, Feldt-Rasmussen U, Fliers E, et al. European Thyroid Association (ETA) guidelines on the diagnosis and management of central hypothyroidism. Eur Thyroid J 2018;7(5):225–37.

[25] Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism–pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 2015;11(9):547–64.

[26] Nanduri VR, Stanhope R. Why is the retention of gonadotrophin secretion common in children with panhypopituitarism due to septo-optic dysplasia? Eur J Endocrinol. 1999;140(1):48–50.

[27] Hanna CE, Mandel SH, LaFranchi SH. Puberty in the syndrome of septo-optic dysplasia. Am J Dis Child 1989;143(2):186–9.

[28] Fitz CR. Holoprosencephaly and septo-optic dysplasia. Neuroimaging Clin N Am 1994;4(2):263–81.

[29] Bauer HG. Endocrine and other clinical manifestations of hypothalamic disease; a survey of 60 cases, with autopsies. J Clin Endocrinol Metab 1954;14(1):13–31.

[30] Gan HW, Phipps K, Aquilina K, Gaze MN, Hayward R, Spoudeas HA. Neuroendocrine morbidity after pediatric optic gliomas: a longitudinal analysis of 166 children over 30 years. J Clin Endocrinol Metab 2015;100(10):3787–99.

[31] Alyahyawi N, Dheensaw K, Islam N, Aroichane M, Amed S. Pituitary Dysfunction in pediatric patients with optic nerve hypoplasia: a retrospective cohort study (1975-2014). Horm Res Paediatr 2018;89(1):22–30.

[32] Stanhope R, Hindmarsh P, Kendall B, Brook CG. High resolution CT scanning of the pituitary gland in growth disorders. Acta Paediatr Scand 1986;75(5): 779–86.

[33] Maghnie M, Ghirardello S, Genovese E. Magnetic resonance imaging of the hypothalamus-pituitary unit in children suspected of hypopituitarism: who, how and when to investigate. J Endocrinol Invest 2004;27(5):496–509.

[34] Garcia-Filion P, Epport K, Nelson M, Azen C, Geffner ME, Fink C, et al. Neuroradiographic, endocrinologic, and ophthalmic correlates of adverse developmental outcomes in children with optic nerve hypoplasia: a prospective study. Pediatrics 2008;121(3):e653–9.

[35] Dahl S, Kristoffersen Wiberg M, Tear Fahnehjelm K, Savendahl L, Wickstrom R. High prevalence of pituitary hormone deficiency in both unilateral and bilateral optic nerve hypoplasia. Acta Paediatr 2019;108(9):1677–85.

[36] Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, et al. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet 2001;357(9254):425–31.

[37] Pappachan JM, Raskauskiene D, Kutty VR, Clayton RN. Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. J Clin Endocrinol Metab 2015;100(4):1405–11.