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\textsuperscript{+} and SOD\textsuperscript{-} indicate patients with or without hypopituitarism, respectively.

Findings: All deficits were more frequent and occurred earlier in MPHD than SOD\textsuperscript{+} [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\% vs 41\%], 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\textsuperscript{+} 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\textsuperscript{+} 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.

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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.
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 abnormalities 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. Ethics

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 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.
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 using Kruskal–Wallis, ANOVA or chi-square, as appropriate. Where 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.

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) | (5.32–21.00) | (4.66–21.48) | (1.03–15.01) | |
| Obesity at last appointment n (%) | 51/161 (31.1) | 21/51 (41.2) | 4/33 (12.1) | 0.015 |
| 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.

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 (68% for SOD, 56% for MPHD, and 47% for ONH), and 3.2% (131) in isolated ONH. No mortality was recorded in MPHD. In none of the deceased patients was the endocrine morbidity record 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.

3.1.2. 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 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 Gn [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 (33.3%) had pituitary stalk (PS) abnormalities (1 absence and 2 thinness). 1/12 (9.1%) had the Posterior 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).
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 2.55–16.44 years). All had SAP, 2 had posterior pituitary absence (PPA) and 1 had PSIS [SAP + Ectopic Posterior Pituitary (EPP) + Pituitary stalk Absence (PSA)].

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 PSH thickening were documented in the SOD+ group only (Table 3).

Half of patients with isolated ONH and 73% 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%) MPHD had MPHD. Four of them had multiple pituitary defects, EPP+PSA within the under-virilised genitalia subgroup that are significantly associated with the EMS [HR 4.08 (2.05–8.00), p=0.0015]. Genetic variants were identified in these groups.

3.4. Molecular diagnoses

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.

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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), LH/X4 (n=1), and GL2 (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.
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; (2) 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/leaness.

Figure 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 Deficits; GH: Growth Hormone, TSH: Thyroid-Stimulating Hormone; ACTH: AdrenoCorticoTropic Hormone; Gn: Gonadotrophin; CI: confidence interval; yrs: years.

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

<table>
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<tr>
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<th>SOD (n:171)</th>
<th>MPHD (n:53)</th>
<th>ONH (n:35)</th>
<th>p value</th>
<th>Percentage difference</th>
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<td>SPP: Slowly-progressing</td>
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<td>square. * SOD vs MPHD.</td>
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<td>vs ONH.</td>
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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-).

<table>
<thead>
<tr>
<th></th>
<th>SOD (n:171)</th>
<th>MPHD (n:53)</th>
<th>ONH (n:35)</th>
<th>SOD+ (n:132)</th>
<th>SOD- (n:39)</th>
<th>p value*</th>
<th>Percentage difference</th>
<th>Confidence interval</th>
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</thead>
<tbody>
<tr>
<td>AP abnorm</td>
<td>135/162 (83.3)</td>
<td>49/50 (98.0)</td>
<td>17/34 (50.0)</td>
<td>108/125 (86.4)</td>
<td>27/37 (73.0)</td>
<td>0.127</td>
<td>11.6</td>
<td>-1.8, 18.9</td>
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<td></td>
<td>n (%)</td>
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<tr>
<td>AP Absence</td>
<td>2/162 (1.2)</td>
<td>1/50 (2.0)</td>
<td>0/34 (0.0)</td>
<td>2/125 (1.6)</td>
<td>0/37 (0.0)</td>
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<tr>
<td>Small AP (SAP)</td>
<td>132/162 (81.5)</td>
<td>48/50 (96.0)</td>
<td>17/34 (50.0)</td>
<td>105/125 (84.0)</td>
<td>27/37 (73.0)</td>
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<tr>
<td>AP Enlargement</td>
<td>1/162 (0.6)</td>
<td>0/50 (0.0)</td>
<td>0/34 (0.0)</td>
<td>1/125 (0.8)</td>
<td>0/37 (0.0)</td>
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<tr>
<td>PP abnorm</td>
<td>96/161 (59.3)</td>
<td>43/50 (86.0)</td>
<td>0/34 (0.0)</td>
<td>84/125 (67.2)</td>
<td>12/37 (32.9)</td>
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<td>n (%)</td>
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<tr>
<td>PP Absence (PPA)</td>
<td>34/162 (21.0)</td>
<td>3/50 (6.0)</td>
<td>0/34 (0.0)</td>
<td>27/125 (21.6)</td>
<td>7/37 (18.9)</td>
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<tr>
<td>PP Hypoplasia</td>
<td>8/162 (4.9)</td>
<td>0/50 (0.0)</td>
<td>0/34 (0.0)</td>
<td>4/125 (3.2)</td>
<td>4/37 (10.8)</td>
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<tr>
<td>PP Enlargement</td>
<td>1/162 (0.6)</td>
<td>0/50 (0.0)</td>
<td>0/34 (0.0)</td>
<td>1/125 (0.8)</td>
<td>0/37 (0.0)</td>
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<tr>
<td>Ectopic PP (EPP)</td>
<td>53/162 (32.7)</td>
<td>40/50 (80.0)</td>
<td>0/34 (0.0)</td>
<td>52/125 (41.6)</td>
<td>1/37 (2.7)</td>
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<tr>
<td>PS abnorm</td>
<td>78/157 (49.7)</td>
<td>23/49 (46.9)</td>
<td>0/34 (0.0)</td>
<td>67/122 (54.9)</td>
<td>11/35 (31.4)</td>
<td>0.629</td>
<td>8.0</td>
<td>-8.3, 23.7</td>
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<td></td>
<td>n (%)</td>
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<tr>
<td>PS Absence (PSA)</td>
<td>32/157 (20.4)</td>
<td>11/49 (25.4)</td>
<td>0/34 (0.0)</td>
<td>30/122 (24.6)</td>
<td>2/35 (5.7)</td>
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<tr>
<td>Thin PS</td>
<td>43/157 (27.4)</td>
<td>10/49 (20.4)</td>
<td>0/34 (0.0)</td>
<td>34/122 (27.9)</td>
<td>9/35 (25.7)</td>
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<tr>
<td>Interrupted PS</td>
<td>2/157 (1.3)</td>
<td>2/49 (4.1)</td>
<td>0/34 (0.0)</td>
<td>2/122 (1.6)</td>
<td>0 (0.0)</td>
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<tr>
<td>Thick PS</td>
<td>1/157 (0.6)</td>
<td>0/49 (0.0)</td>
<td>0/34 (0.0)</td>
<td>1/122 (0.8)</td>
<td>0 (0.0)</td>
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<tr>
<td>Pituitary Stalk Interruption Syndrome (PSIS)</td>
<td>37/159 (23.3)</td>
<td>23/49 (46.9)</td>
<td>0/34 (0.0)</td>
<td>36/122 (29.5)</td>
<td>1/37 (2.7)</td>
<td>0.030</td>
<td>17.4</td>
<td>1.6, 33.0</td>
</tr>
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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.
Although MPHD exhibit an earlier onset of deficiencies, 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 deficiencies. Such association has previously been documented in patients with PSIS [20].

Asynchronous evolution of deficiencies 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
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]. 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.

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]. 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.
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 MPH) in three SOD and one MPH 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 MPH, 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 meta-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, MPH 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, MPH and ON development are responsible for a 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 MPH. 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 MPH. ON and H-P abnormalities are the core features of the so-called “Septo-Optic Dysplasia” syndrome, whilst additional midline (corpus callosum) or hemispheric brain abnormalities may or not be present, with linked 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.

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Supplementary materials

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

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