SPHINGOSINE 1- PHOSPHATE LYASE INSUFFICIENCY SYNDROME (SPLIS) AS A CAUSE OF PRIMARY ADRENAL INSUFFICIENCY AND PRIMARY HYPOGONADISM

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INTRODUCTION

- Sphingosine 1-phosphate lyase insufficiency syndrome (SPLIS) was initially described in 2017 as a novel condition affecting sphingolipid metabolism.
- Presenting features: nephrotic syndrome and primary adrenal insufficiency (PAI) and to a lesser extent ichthyosis, neurological disease and lymphopenia.
- Additional endocrine presentation with primary hypothyroidism and primary hypogonadism.

AIM

To interrogate the endocrine aspect of the syndrome we reviewed clinical data within our patient cohort with SPLIS and those within the wider literature.

METHOD

- Literature review on published clinical case reports was done on pubmed using search terms “SGPL1 deficiency” and “S1P lyase deficiency”.
- Patient data were retrieved from our previously collected cohort database.

RESULTS

- Total of 45 published cases to date.
- SPLIS is associated with high mortality (n=23/45, 51%; 4 of these *in utero*).
- Approximately 64% of patients (n=29/45) presented with at least one form of endocrinopathy, PAI being the most common presentation (Figure 1).
- The vast majority of those with PAI also had nephrotic syndrome (86%).
- Amongst 3 kindreds, 3 patients presenting with PAI alone, and 1 patient with PAI and neurological disease, shared the same *SGPL1* mutation, c.665 G>A; p.Arg222Gln. Nevertheless, 6 other patients with this mutation manifested both PAI and nephrotic syndrome.
- No clear genotype-phenotype correlations observed (Figure 2).

Figure 1

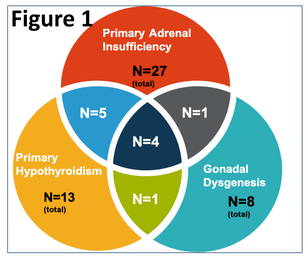

Figure 1: Breakdown of patients’ presenting endocrinopathies

Adrenal and Gonadal disease:

- Patients’ characteristics are summarized for adrenal and gonadal presentation (Table 1).
- 5 additional patients had evidence of adrenal calcifications on imaging, but no biochemical testing was done.
- There are no reports of pubertal delay in female patients.
- Female patients of age within our cohort have normal ovarian reserve as evidenced by AMH levels (n=2).

Figure 2

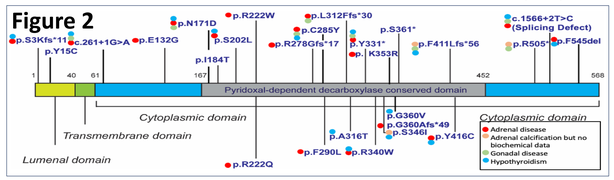

Figure 2:
A topology of all published *SGPL1* mutations in SPLIS.

Table 1: Patients’ Characteristics	**Primary adrenal disease (~60%)**	**Primary gonadal disease (~18%)**
Age of Onset	Range= 0-11 yr Median= 1.17 yr	All were diagnosed during neonatal period.
Sex	Male: Female Ratio 2:1	Males Only
Clinical features/ Imaging findings	Adrenal Calcifications (n=13/15, 87%) Enlarged Adrenal (n=2/15, 13%)	Microphallus (n=7/8) Cryptorchidism (n=8/8)
Biochemical features	Glucocorticoid deficiency= 27/27 Mineralocorticoid deficiency=7/27	- Raised basal LH and FSH ↑ - exaggerated response to LHRH stimulation ↑ - a lack of testosterone response to HCG stimulation ↓ - low antimullerian hormone (AMH) ↓
Mortality	Approx. 44% (n=12/27) median age= 1.4 yr	100% (n=8/8); median age = 0.25 yr.

CONCLUSIONS

- SPLIS is unique amongst sphingolipid disorders in presenting with significant endocrinopathy.
- Endocrine dysfunction needs to be considered at diagnosis and surveillance undertaken for evolving disease.
- SPLIS should also be considered in the differential diagnosis of PAI alone.

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