A retrospective analysis of the prevalence of imprinting disorders in Estonia: updated results

M. Yakoreva[1,2], T. Kahre[1,2], E. Õiglane-Shlik[3], M.-A. Vals[1,2,3], P. Mee[4], K. Õunap[1,2]

[1] Department of Clinical Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia
[2] Department of Clinical Genetics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia
[3] Children's Clinic, Tartu University Hospital, Tartu, Estonia
[4] United Laboratories, Tartu University Hospital, Tartu, Estonia

Introduction

- Imprinting disorders (IDs) are a small group of rare congenital diseases affecting mainly growth, development, metabolism and behaviour. The cause of IDs is an aberrant expression of imprinted genes due to genetic or epigenetic abnormalities.
- At present, at least twelve clinically recognized IDs are known. Because of high variability of clinical phenotype and molecular alterations, the exact prevalence of IDs is not known.

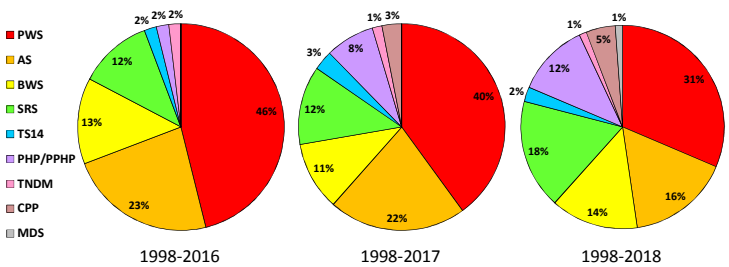
Methods

- In this study we retrospectively reviewed records of all Estonian patients with both molecularly and clinically diagnosed IDs found during the period 1998-2018. A prospective study was also conducted, in which all patients with clinical suspicion of ID were molecularly analyzed.
- Molecular tests for IDs were performed in the molecular diagnostics laboratory of Department of Clinical Genetics in Tartu University Hospital.
- During the period 1998-2018 a total of 931 ID analyses were carried out; 641 of them were tests for Prader-Willi/Angelman syndrome (PWS/AS), 219 for Beckwith-Wiedemann/Silver-Russell syndrome (BWS/SRS) and 71 for other IDs.

Results

- Genetic or epigenetic alterations were identified in 6.4% of all performed PWS/AS tests and in 7.3% of BWS/SRS tests.
- A total of 86 individuals with IDs were identified:
  - 27 (31.5%) - Prader-Willi syndrome (PWS)
  - 14 (16%) - Angelman syndrome (AS)
  - 15 (17.5%) - Silver-Russell syndrome (SRS)
  - 12 (14%) - Beckwith-Wiedemann syndrome (BWS)
  - 10 (12%) - Pseudo- and pseudopseudohypoparathyroidism (PHP/PPHP)
  - 4 (5%) - Central precocious puberty (CPP)
  - 2 (2%) - Temple syndrome (TS14)
  - 1 (1%) - Transient neonatal diabetes mellitus (TNDM)
  - 1 (1%) - Myoclonus-dystonia syndrome (MDS)
- No cases of Kagami-Ogata syndrome or maternal uniparental disomy of chromosome 20 have been found.
- 1/3 of all SRS and BWS cases fulfilled diagnostic criteria for these disorders, but were negative for genetic abnormalities.
- Age at diagnosis varied from prenatal to 83 years.

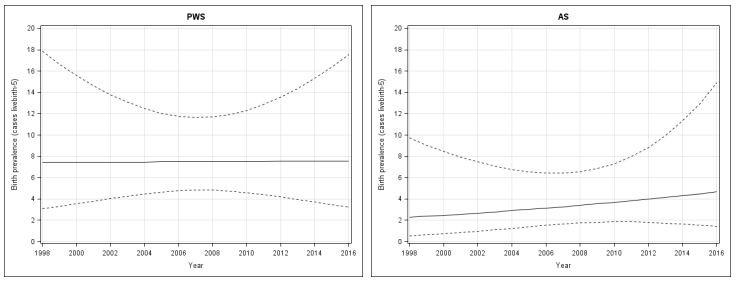
Fig. 1: Pie charts showing the percentage of all molecularly and clinically diagnosed IDs in Estonia during the periods 1998-2016, 1998-2017 and 1998-2018.



- All cases of PHP/PPHP, CPP, TS14, TNDM, MDS and the most cases of SRS and BWS were diagnosed in the last 6 years due to improved diagnostic methods and increased physicians' awareness. The percentage of these rare IDs dramatically increased during the last few years (Fig. 1).

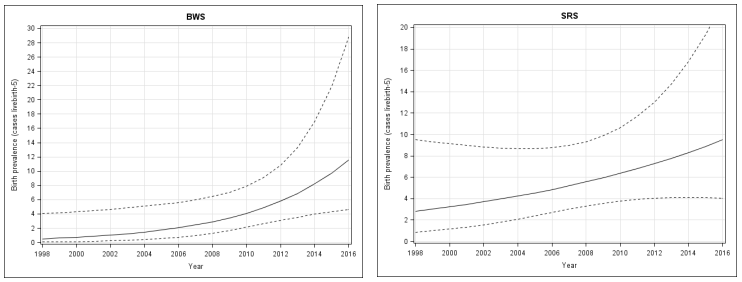
- The total prevalence of IDs in Estonia is 5.1/100,000.
- During the period 2004-2016 birth prevalence of most frequent IDs in Estonia was:
  - PWS 1/13,599 live births (1/10,000-1/25,000)
  - AS 1/27,198 (1/12,000-1/20,000)
  - BWS 1/21,154 (estimated ~1/15,000)
  - SRS 1/15,866 (1/75,000-1/100,000)
  - PHP/PPHP 1/27,198 (prevalence is not known)
- The obtained results only partially correlate with previously published data [1-5].
- There was no statistically significant increase in birth prevalence of PWS and AS during the last 19 years (Fig. 2). It stayed on the level reached at the end of our previous study of AS/PWS and showing the effectiveness of this epidemiological approach [1.]

Fig. 2: Distribution of PWS and AS birth prevalence in Estonia from 1998 to 2016 by statistical logit analysis. The dashed lines indicate the 95% confidence interval.



- The birth prevalence of BWS and SRS has significantly increased during the last decade (Fig. 3).

Fig. 3: Distribution of BWS and SRS birth prevalence in Estonia from 1998 to 2016 by statistical logit analysis. The dashed lines indicate the 95% confidence interval.



Conclusions

- The birth prevalence of PWS has been found to be as expected,
- The prevalence of AS and BWS was ~1.5 times lower in comparison with PWS.
- Probably the real worldwide prevalence of SRS is underestimated and may be at least 4 times higher than expected.
- The GNAS-gene-related IDs (PHP/PPHP) may also be relatively frequent disorders.

This work was supported by the Estonian Research Council grant PUT355 and University of Tartu's baseline funding.

References

1. Õiglane-Shlik E et al. Prevalence of Angelman syndrome and Prader–Willi syndrome in Estonian children: sister syndromes not equally represented. American Journal of Medical Genetics 2006. Part A 140A:1936–1943.
2. Mackay DJG et al. Multilocus methylation defects in imprinting disorders. BioMol Concepts 2015. 6(1): 47–57.
3. Eggermann T et al. Congenital imprinting disorders: EUCID.net - a network to decipher their aetiology and to improve the diagnostic and clinical care. Clin Epigenetics 2015. Mar 14;7(1):23.
4. Mackay DJG et al. Human imprinting disorders: Principles, practice, problems and progress. European Journal of Medical Genetics 60 (2017) 618-626.
5. Barisic et al. Beckwith Wiedemann syndrome: A population-based study on prevalence, prenatal diagnosis, associated anomalies and survival in Europe. European Journal of Medical Genetics (2018).