NO PHOTOGRAPHY
OR SOCIAL MEDIA SHARING

The authors of this paper are not yet ready to share the results of this study beyond this meeting. No photography or social media sharing is allowed on this paper.
Thank you.
DSS Case 2022-7

• I have no financial disclosures.
Learning Objectives:

- Following the presentation, the learner will recall the first gene discovered in association with the diagnosis discussed.

- Following the presentation, the learner will be able to identify the most common neuropathologic abnormalities associated with the diagnosis discussed.
Clinical History (2022-7)

• History: 11 yo F with global developmental delay, seizures, cerebral palsy, and nephrotic syndrome. Family history of a similar condition. Succumbs to an infection / coagulopathy.

• Autopsy findings:
  • Microcephaly, dysmorphic facies
  • Malrotation of extremities and dorsiflexed feet
  • Surgical absence one kidney, thrombus vena cava

• Neuropathology findings:
  • 470 gram brain with mildly dilated ventricles and firm, small cerebellum
Gross photos (2022-7)
DIAGNOSIS?
Differential Diagnosis
Childhood Cerebellar Atrophy

**Inherited**
- Ataxia telangiectasia
- Spinocerebellar atrophy
- Infantile neuroaxonal dystrophy
- Lysosomal disorders
- Mitochondrial disorders
- Neuronal ceroid lipofuscinosis
- Many more...

**Acquired**
- Posterior fossa malformation
- Posterior fossa tumor, therapy
- Cerebellar hemorrhage / ischemia
- Immune-mediated
- Paraneoplastic syndrome
- Infection (viral)
- Medication/exogenous toxin
Clinically suspected diagnosis:
Galloway-Mowat Syndrome (GAMOS)

• Microcephaly and nephrotic syndrome, first described in 1968
• Multiple genes identified since 2014
  • GON7, LAGE3, NUP107, **NUP133, OSGEP, PRDM15, TP53RK, TPRKB, WDR73, WDR4, and YRDC**
• Variable constellations of neuropathologic findings
  • Most common: Small brain weight for age
  • Other findings: abnormal gyration (pachygyria), cortical lamination defects, cerebellar hypoplasia / atrophy, hippocampal changes, optic nerve gliosis and hypoplasia / atrophy of lateral geniculate nucleus, glioneuronal heterotopias, leptomeninges, gray matter heterotopia, hypomyelination, changes of inferior olivary nuclei
  • Of note: cerebellar smallness documented prenatally (32 wks ga)

**Green**: affected genes with previously published neuropathologic findings
**Red**: current case
Genetic testing

• Targeted NGS of genes associated with Galloway-Mowat Syndrome
  • GON7, LAGE3, NUP107, NUP133, OSGEP, PRDM15, TP53RK, TPRKB, WDR73, WDR4, and YRDC

• Results:
  • Two heterozygous variants on OSGEP, in *trans*
    • OSGEP c.328T>C, p.Cys110Arg (previously published)
    • OSGEP c.365G>T, p.Gly122Val (novel)

• Diagnosis: Galloway-Mowat Syndrome 3
GAMOS 3, OSGEP

• **OSGEP** is the catalytic subunit of the KEOPS-complex
  • **Kinase, Endopeptidase and Other Proteins of Small size**

• Functions of KEOPS-complex:
  • Regulation of tRNA modification (t^6^A) required for accurate and efficient translation
  • Telomere length
    • Role in telomere-associated DNA-damage response (potentially linked to microcephaly)
  • Genome maintenance

• OSGEP knockdown (zebrafish, mouse embryo) → primary microcephaly, early death
  • Impaired growth of yeast and cell proliferation in human podocyte cell lines
References


Digital Neuropathology @ Pitt
Thank you!

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  • Matthew Kilpatrick, MD
  • Nicholas Batalis, MD
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