Fetal Origins of Autism Spectrum Disorders
Fetal Neuro-programming

Hind Moussa, M.D., FACOG
No relevant conflicts of interest to report
Autism Spectrum Disorders (ASD)

- Difficulties:
  - Social interaction
  - Verbal and nonverbal communication
  - Repetitive behaviors

- USA-ASD prevalence 1-2%

- ASD affects 1 in 59 children

- 4x more common in boys
Prevalence in Lebanon

<table>
<thead>
<tr>
<th>Gender</th>
<th>Prevalence ASD, according to M-CHAT N (%)</th>
<th>Prevalence ASD corrected (M-CHAT prevalence*0.058) %</th>
<th>Prevalence ASD (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>263 (26.4)</td>
<td>1.53</td>
<td>0.77–2.29</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>144 (26.8)</td>
<td>1.55</td>
<td>0.51–2.59</td>
</tr>
<tr>
<td>Female</td>
<td>118 (25.7)</td>
<td>1.49</td>
<td>0.38–2.60</td>
</tr>
<tr>
<td>Governorate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beirut</td>
<td>66 (30.4)</td>
<td>1.76</td>
<td>0.01–3.51</td>
</tr>
<tr>
<td>Mount Lebanon</td>
<td>197 (25.2)</td>
<td>1.46</td>
<td>0.62–2.30</td>
</tr>
</tbody>
</table>
• Early human brain development
  • Sequence of intricate processes
  • Functionally operative neural circuits

• Developmental trajectories of early brain network formation
  • Genetically programmed
  • Epigenetic influences
  • Environmental influences
GW4-6
– GW5 nascent cerebral hemispheres can be seen
– Symmetric cell division of neuroepithelial stem cells, which become ventricular radial glia cells

GW 6-10
– GW6 neurogenesis of first wave destined for cortical plate
– GW7-10 neurogenesis and neuronal migration to cortical plate
– Neural progenitor cells = radial glia in VZ
– Asymmetric cell division: separating proliferating cells from postmitotic neurons

Dividing cells generate pairs of daughter cells
• with the same symmetric cell fate (Two progenitor cells)
• with distinct, asymmetric cell fates (one progenitor and one neuron)
Neuronal Migration

Radial unit - new

Neuronal Migration

Pasko Rakic

Migration


Embryonic Age

Model #3
Rakic/Leydon
Based: Rakic, Science, 1974, 1988

VZ

IZ

PP
<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategories</th>
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<tbody>
<tr>
<td>1. Fetal Factors</td>
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</tr>
<tr>
<td>2. Placental Factors</td>
<td></td>
</tr>
<tr>
<td>3. Maternal Factors</td>
<td></td>
</tr>
<tr>
<td>1. The Passenger</td>
<td></td>
</tr>
<tr>
<td>2. The Placenta</td>
<td></td>
</tr>
<tr>
<td>3. The Parent</td>
<td></td>
</tr>
</tbody>
</table>
Congenital Heart Disease
Fetal Brain Oxygenation and Perfusion in Congenital Heart Disease: Impact on Neurodevelopment

![Diagram showing prevalence of neurodevelopmental impairment across different levels of congenital heart disease complexity.](image-url)
Fetal Brain Oxygenation and Perfusion in CHD

Neurodevelopmental Sequelae of CHD

Why does it happen?

Abnormal fetal circulation

Compromise in utero

Compromise at delivery

Surgery
CPB/Circulatory arrest

Chronic cyanosis
Cardiac dysfunction
Arrhythmias

Preoperative compromise

Postoperative hypotension/hypoxia
Brain Development and Injury in CHD: Benefit of Prenatal Diagnosis

- Preop injury and postop brain development in TGA/SV
  - Brain injury less in those with prenatal dx (24 vs 48%)
  - More rapid brain development postop in those with a prenatal diagnosis

Table 3. Prevalence of Preoperative Brain Injury by Cardiac Diagnosis and Postnatal vs Prenatal Diagnosis of Critical Congenital Heart Disease

<table>
<thead>
<tr>
<th>Preoperative Brain Injury and Cardiac Diagnosis</th>
<th>No. With Injury/Total No. With Cardiac Diagnosis (%)</th>
<th>Postnatal Diagnosis</th>
<th>Prenatal Diagnosis</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any injuryb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>41/86 (48)</td>
<td>16/67 (24)</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>TGA</td>
<td>31/68 (46)</td>
<td>6/28 (21)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>SVP</td>
<td>10/18 (56)</td>
<td>10/39 (26)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>SVP with aortic arch obstruction</td>
<td>9/17 (53)</td>
<td>7/31 (23)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>White matter injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA</td>
<td>17/68 (25)</td>
<td>3/26 (11)</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>SVP</td>
<td></td>
<td></td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>TGA</td>
<td></td>
<td></td>
<td>.61</td>
<td></td>
</tr>
<tr>
<td>SVP</td>
<td></td>
<td></td>
<td>.71</td>
<td></td>
</tr>
<tr>
<td>Hypoxic-ischemic injury</td>
<td></td>
<td></td>
<td>.32</td>
<td></td>
</tr>
</tbody>
</table>

Prenatal diagnosis, delivery room care, and fetal treatment to improve O2 delivery

Peyvandi, JAMA Pediatrics 2016
Intrauterine Environment

1. Fetal Factors
   2. Placental Factors
   3. Maternal Factors

1. The Passenger
   2. The Placenta
   3. The Parent
The Growth Restriction Intervention Trial (GRIT)

A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation

The GRIT Study Group*

Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial

The GRIT study group*
### GRIT Studies, 2003, 2004, 2010

**BJOG 2003**
- Immediate delivery
  - C-section: 91% < 0.05 76%
  - FDIU: 2 < 0.05 9
  - Neonatal Death: 27 0.06 18
  - Perinatal Mortality: 29 n.s. 27
- Prematurity-related: 17 < 0.05 8

**Lancet 2004**
- "2 year Follow-up: Griffith DQ, CP, Mortality"
  - Developmental delay: 14 < 0.05 5
  - Cerebral palsy: 8 < 0.01 0

**AJOG 2010**
- "6-13 year Follow-up: Kaufmann ABC, Cognitive Outcome"

**Identical Long-term outcomes**

547 singleton/Twins - 24-36 GA

- Unsure about delivery timing
  - +4.9 days (*6.9 > 31 SSW)
  - Deliver when no longer in doubt

<30 weeks
Trial Of Randomized Umbilical And Fetal Flow In Europe (Truffle)

Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE)


2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial

Christoph C Lees, Neil Marlow, Alaid van Wasenaer-Leemhuis, Birgit Arabin, Caterina M Bilardo, Christoph Brezinka, Sandra Calvert, Jan B Derks, Anke Diemert, Johannes J Duvekot, Enrico Ferrazzi, Tiziana Frusca, Wessel Ganzervoort, Kurt Hecher, Pasquale Martinelli, Eva Ostermayer, Aris T Papageorgiou, Dietmar Schlembach, KTM Schneider, Baskaran Thilaganathan, Tuilla Todros, Adriana Valcamonico, Gerard H A Visser, Hans Wolf, for the TRUFFLE study group#

A conservative approach to timing delivery in waiting for late Ductus Venosus changes, unless severe CTG changes occur first, was associated with a more favorable 2 year outcome in early onset fetal growth restriction.
1. Fetal Factors
2. Placental Factors
3. Maternal Factors

1. The Passenger
2. The Placenta
3. The Parent
<table>
<thead>
<tr>
<th>Maternal Conditions</th>
<th>OR</th>
<th>Confidence Interval</th>
<th>Study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Eclampsia</td>
<td>1.5**</td>
<td>1.18-4.68</td>
<td>CHARGE Population Study</td>
<td>JAMA Pediatr. 2014 Dec 8.</td>
</tr>
<tr>
<td>Maternal thyroid peroxidase antibody positivity (TPO-Ab+)</td>
<td>2.6</td>
<td>1.16–2.75</td>
<td>Nested case-control design of the Finnish Prenatal Study of Autism (FiPS-A)</td>
<td>Prog Neuropsychopharmacol Biol Psychiatry. 2015 Mar 3;57:86-92.</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>2.36</td>
<td>1.07–2.54</td>
<td>The study cohort consisted of all of the children born in Denmark from 1993 through 2004 (689 196 children).</td>
<td>Pediatrics 124: 687–694</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>2.12</td>
<td>1.27–5.75</td>
<td>The study cohort consisted of all of the children born in Denmark from 1993 through 2004 (689 196 children).</td>
<td>Pediatrics 124: 687–694</td>
</tr>
<tr>
<td>Type I Diabetes</td>
<td>1.86</td>
<td>1.07–3.77</td>
<td>The study cohort consisted of all of the children born in Denmark from 1993 through 2004 (689 196 children).</td>
<td>Pediatrics 124: 687–694</td>
</tr>
<tr>
<td>Febrile Episode</td>
<td>1.84</td>
<td>1.1-2</td>
<td>Danish Cohort</td>
<td>Pediatrics. 2012 Dec;130(6):e1447-54.</td>
</tr>
</tbody>
</table>
Association of Autism with Maternal Infections, Perinatal and Other Risk Factors: A Case-Control Study

Dikran Richard Guisso¹ · Fadi S. Saadeh¹ · Dahlia Saab² · Joud El Deek¹ · Sarah Chamseddine¹ · Hadi Abou El Hassan¹ · Ghidaa Majari¹ · Rose-Mary Boustany²,³
Parental Inheritance of Endothelial Nitric Oxide Synthase (eNOS) Gene and Abnormal Uterine Environment Contribute to Autism Spectrum Disorders in a Hypertensive Murine Model

Hind Moussa, Baha Sibai, Sean Blackwell, Mateo Leon, John Redell, Yin Liu, Pramod Dash, Monica Longo

Division of Maternal Fetal Medicine
Department of Obstetrics, Gynecology and Reproductive Sciences
UT Health- University of Texas Medical School at Houston
Maternal Factors → Uterine Environment

Maternal and Paternal Genes

HYPERTENSION

20%

ZYGOTE

PHENOTYPE
Mice Offspring Developing in an Abnormal Uterine Environment, Secondary to Maternal Hypertension, Will Have an ASD-Like Phenotype
1. To evaluate the contribution of maternal hypertension to ASD-like phenotype

2. To identify novel ASD related genes and their biological processes in the cerebellum
Endothelial Nitric Oxide Synthase (eNOS) Hypertension Mouse Model

Knock Out eNOS-/-

Wild Type eNOS+/+

Heterozygous Offspring eNOS-/+
Cross Breeding Scheme

Knock Out eNOS-/- Hypertensive Mother

Wild Type eNOS+/+

Heterozygous Mat-eNOS-/+
Knock Out eNOS-/-
Hypertensive Mother

Cross Breeding Scheme

Wild Type eNOS+/+

Abnormal Uterine Environment

Heterozygous Mat-eNOS-/+
Cross Breeding Scheme

Wild Type eNOS+/+  Knock Out eNOS-/-
Normotensive Mother

Heterozygous Pat-eNOS-/+
Cross Breeding Scheme

Wild Type eNOS+/+ Normotensive Mother

Knock Out eNOS-/-

Normal Uterine Environment

Heterozygous Pat-eNOS-/+
Heterozygous Offspring

Developed in an Abnormal Uterine Environment
Hypertensive Mother

Genetically Identical Offspring

Developed in a Normal Uterine Environment
Normotensive Mother

Heterozygous Mat-eNOS-/+  

Heterozygous Pat-eNOS-/+
Heterozygous Offspring

Developed in an Abnormal Uterine Environment
Hypertensive Mother

Developed in a Normal Uterine Environment
Normotensive Mother

Heterozygous Mat-eNOS-+/+

Heterozygous Pat-eNOS-+/+

ASD Features
Behavioral Phenotype Characterization
### ASD Behavioral Tests

<table>
<thead>
<tr>
<th>Social Behavior</th>
<th>Repetitive Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sociability</td>
<td>- Open Field</td>
</tr>
<tr>
<td>- Preference For Social Novelty</td>
<td>- Marble Burying</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxiety Behavior</th>
<th>Motor Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Light/Dark Box</td>
<td>- Beam Balance</td>
</tr>
<tr>
<td>- Elevated Plus Maze</td>
<td>- Rotor Rod</td>
</tr>
<tr>
<td>- Open Field</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Spatial Learning and Memory</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>- Morris Water Maze</td>
<td></td>
</tr>
</tbody>
</table>

2-way-RM-ANOVA, 1-way-ANOVA, t-test, P<0.05 significant
ASD Behavioral Tests - Sociability

[Graph showing time totals for different groups (Mat-eNOS-/+ and Pat-eNOS-/+ vs. WT) across object, mouse, and center categories. The graph includes error bars indicating variability.]
Morris Water Maze
Spatial Learning and Memory
Morris Water Maze
Spatial Learning and Memory

Latency (sec)

Trial (1-12) in 2 trial block

Mat-eNOS-/-+
Pah-eNOS-/-+
WT
## ASD Behavioral Tests

<table>
<thead>
<tr>
<th></th>
<th>Wild-Type</th>
<th>Pat-eNOS-/+</th>
<th>Mat-Enos-/+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Social Behavior</strong></td>
<td>Preference For Novelty</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Repetitive Behavior</strong></td>
<td>Open Field</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Anxiety Behavior</strong></td>
<td>Light Dark Box</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Spatial Learning And Memory</strong></td>
<td>Morris Water Maze</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>Motor Function</strong></td>
<td>Beam Balance/Rotor Rod</td>
<td>↔</td>
<td>↔</td>
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</table>
# ASD Behavioral Tests

<table>
<thead>
<tr>
<th>Behavior Category</th>
<th>Wild-Type</th>
<th>Pat-eNOS-/+</th>
<th>Mat-Enos-/+</th>
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<tr>
<td>Social Behavior</td>
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## ASD Behavioral Tests

<table>
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<th>Behavior</th>
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</tr>
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<td>Motor Function</td>
<td>Beam Balance/Rotor Rod</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>
Identification of ASD Related Genes in the Cerebellum
• Highly conserved structure and function
  • Foliation conserved across evolution

• Structure is “simple”
  • Only 9 principle types of neurons
  • All morphologically distinct
  • Layers and circuitry are stereotyped

• Contains more neurons than rest of brain
  • In mouse, 59/71 million neurons (83%)
  • In human, 69/86 billion neurons (80%)
• **Incidence**
  • Relatively common ~1/5000 live births
  • Can occur in isolation or part of syndrome
  • Genes identified for only a few rare forms

• **Outcome**
  • Most cause DEV delay ± ID ± motor abnormalities
  • ID and ID syndromes, autism, early life epilepsy

• **Prenatal Issues**
  • Most (not all) are visible by GW20
  • Difficult to distinguish by fetal ultrasound/MRI
• Historically
  • Balance
  • Posture
  • Motor control

• Recent
  • External sensory
  • Neocortical circuit refinement

Shaping Higher Function Early In Neurodevelopment
Identification of ASD Related Genes

• RNAs from Mat-eNOS-/+ and Pat-eNOS-/+ cerebella underwent whole transcriptome shotgun sequencing using RNA-Seq

• Differentially expressed genes were examined for pathway analyses to obtain novel ASD related genes

• Gene Ontology enrichment was performed on these novel genes to identify their biologic processes
Gene Ontology Term

Embryo Development
Anatomical Structure Development
Cell Differentiation
Signal Transduction
Autophagy
Carbohydrate Metabolic Process
Catabolic Process
CONCLUSION

• The altered uterine environment, secondary to maternal hypertension, contributes to ASD like features in eNOS heterozygous offspring

• A social deficit, the hallmark of ASD, is differentially present in the offspring of hypertensive mothers

• Novel ASD related genes are differentially expressed between both groups

• ASD etiology has a cerebellar component
Effect of Programmed Maternal Hypertension and Metabolic-like Syndrome during Pregnancy on Offspring Neurodevelopment


Department of Obstetrics, Gynecology and Reproductive Sciences
UTHealth-McGovern Medical School at Houston
1st Generation
Pregnant Female

Wild Type (CTR)

Moderate Hypertension (HTN)

Metabolic Like Syndrome (MLS)

Second Generation Male Wild Type Offspring

Group 1, CTR

Group 2, HTN

Group 3, MLS
# Second Generation Wild Type Offspring

<table>
<thead>
<tr>
<th>Group 1, CTR</th>
<th>Group 2, HTN</th>
<th>Group 3, MLS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Social Behavior</strong></td>
<td><strong>Social Preference</strong></td>
<td><strong>Social Novelty</strong></td>
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<tr>
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<td><img src="image" alt="Green Arrow" /></td>
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<td></td>
<td><img src="image" alt="Red Arrow" /></td>
<td><img src="image" alt="Red Arrow" /></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td><img src="image" alt="Green Arrow" /></td>
<td><img src="image" alt="Green Arrow" /></td>
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<tr>
<td></td>
<td><img src="image" alt="Red Arrow" /></td>
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<td></td>
<td><img src="image" alt="Red Arrow" /></td>
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</tr>
</tbody>
</table>
62: Effect of programmed maternal hypertension and metabolic-like syndrome during pregnancy in offspring neuro-development

Fangxian Lu, Alejandra E. Ontiveros, Hind N. Mousa, Mia M. Saade, Sean C. Blackwell, Pramod Dash, Monica Longo
478: Parental inheritance of NOS3 and uterine environment alter cytokine levels in a murine model of autism like disorder

Hind Moussa, Baha Sibai, Sean Blackwell, Mateo Leon, Anthony Moore, Alissa R. Carver, Maged Costantien, Pramod Dash, Monica Longo

- Blood and brain were collected from KO, KOM, KOP and WT offspring
- N=7-10/group at 12 wks.
- Bio-Plex Mouse Cytokine Assay was run on
  - Serum
  - Cerebellum
  - Hippocampus
- 1-way-ANOVA and t-test were used for statistical analysis.

Pro-Inflammatory Cytokines
- IL-1β, IL-6, IL-17A
- TNF-α, IFN γ

Anti-Inflammatory Cytokines
- IL-10
851: Maternal metabolic syndrome and hypertension altered TNFα and mTOR1 activity in the cerebellum of adult offspring: implications for autism-spectrum disorder

Fangxian Lu, Anthony N. Moore, Danielle Hamrick, Jerrie S. Refuerzo, Baha M. Sibai, Sean C. Blackwell, Pramod Dash, Monica Longo

American Journal of Obstetrics & Gynecology
Volume 216, Issue 1, Pages S487-S488 (January 2017)
DOI: 10.1016/j.ajog.2016.11.760
226: Genes or environment? A novel double knockout mouse model for fetal origins of autism study

Hind N. Moussa, Baha M. Silai, Sean C. Blackwell, David A. Fournie, Alajandra E. Ontiveros, Fangxian Lu, John Redell, Pranee Dash, Monica Longo

Figure 1: Breeding scheme to obtain offspring with and without TSC2 genetic risk born to hypertensive vs. normotensive mothers.
Offspring with and without genetic (TSC2) and environmental risk (HTN) factors performed similarly in behavioral tasks assessing motor function, spatial learning, memory, and anxiety.

Significant interaction between the genetic & environmental risk factors in a social behavior task (P=0.048).

After adjusting for gender, there was a social deficit in males as compared to females, and that deficit was driven by the HTN environmental factor and not the TSC2 genetic risk (Sociability task, male gender P=0.014, eNOS+/− P=0.013, and TSC2+/− P=0.135, interaction of male gender X environmental factor P=0.009).
THE HUMAN PLACENTA PROJECT

http://www.nichd.nih.gov/hpp
UTHSC
OB/Gyn
Monica Longo
Sean Blackwell
Baha Sibai
Mateo Leon
Neuroscience:
Pramod Dash
John Redell
Michael Hylin
Computational Biology
Yin Liu

UTMB
Georges Saade
Maged Costantine
Esther Tamayo

FROM THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON, HOUSTON, TX
AND
THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY AT UNIVERSITY OF TEXAS MEDICAL BRANCH, GALVESTON, TX.
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