Natural History Trial in SLOS

Simona Bianconi, MD

Natural History – Observational Trial

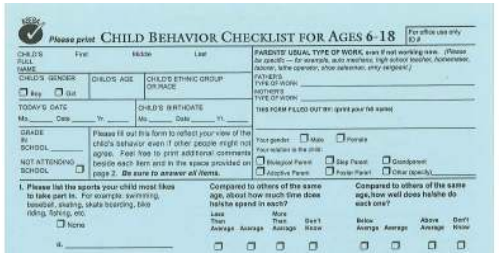
- A study that follows a group of individuals that have or are at risk of developing a certain condition or disease
- The study gathers information on how a certain disease manifests and develops over time
- The goals are
  - Better understanding of disease processes
  - Identifying variations in severity and symptoms
  - Identifying possible treatment approaches
- ➔ The clinical trial can then test the effectiveness of the treatment

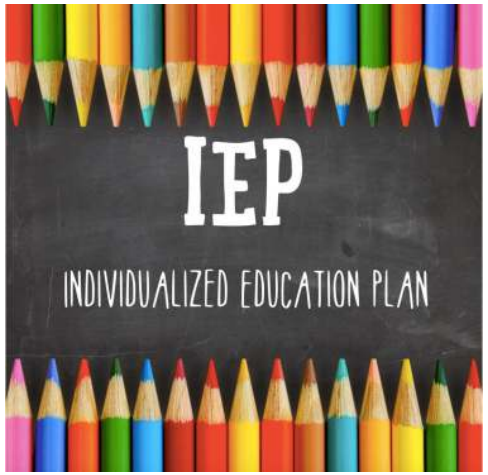
Natural History Study in SLOS

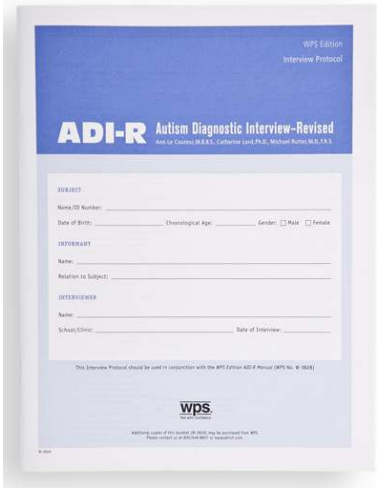
- Trial established in 1998 at NIH
- Systematic assessment of individuals enrolled with same battery of test
- Initially: behavioral testing, overnight EEG, endocrine evaluation with stimulation test, and MRI imaging
- Currently:
  - 112 patients, 63 males

Natural History Study in SLOS

- Neurocognitive/neurodevelopmental testing
  - Dr. Audrey Thurm

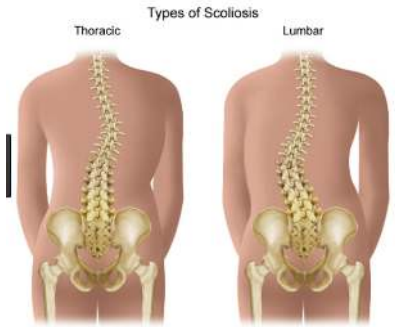






Natural History Study in SLOS

- Physiatry and Rehab medicine (OT, PT)
  - Dr. Paul and Dr. Joe

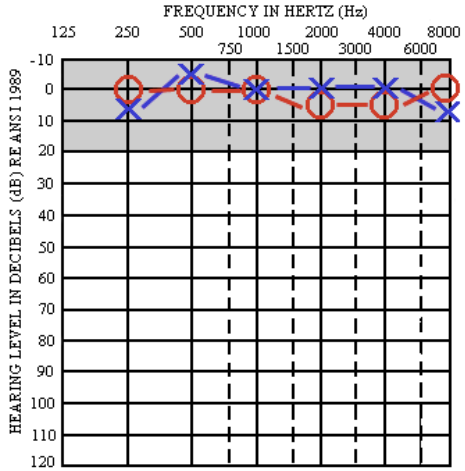


Natural History Study in SLOS

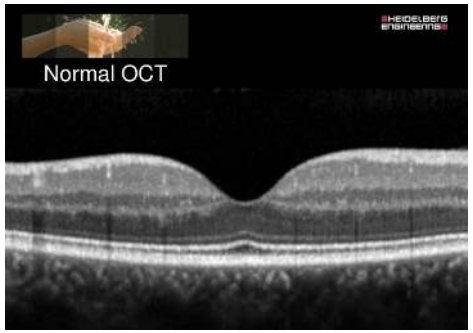
- Speech and Swallow evaluation
  - Beth Solomon
  - Food consistencies
  - Recommendations on oral therapies

Natural History Study in SLOS

- Audiology evaluation

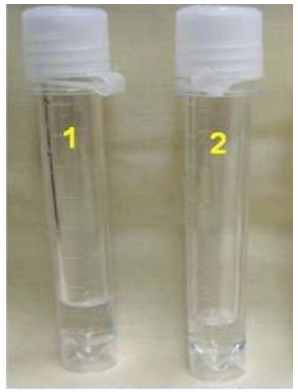


- Ophthalmology evaluation



Natural History Study in SLOS

- Preanesthesia appt
- Skin biopsy
- Lumbar puncture



WEEK OF OCTOBER 9, 2016

Tuesday 10/11/2016

	APPOINTMENT	LOCATION
8:00 am	Consent with Dr. Bianconi	1 NW-Day Hospital
8:30 am	Speech and Swallow Consult Beth Solomon	Radiology
9:00 am		
10:30 am	Vitals	1 NW-Day Hospital
11:00 am	History and Physical Exam	1 NW-Day Hospital
12:30 pm	Preanesthesia Consult Ask for escort	2C-523
1:00 pm		
2:00 pm	Audiology Consult- 2 hours Carmen Brewer	OP5
3:00 pm		
4:00 pm		
5:00 pm	Fasting starting at midnight	

Wednesday 10/12/2016

	APPOINTMENT	LOCATION
8:00am	Vitals, IV-Placement, Fasting blood draw	1 NW-Day Hospital
9:00am		IMC
9:30am		
10:00 am	Lumbar Puncture and Skin Biopsy	IMC
11:00 am	Recovery	1 NW-Day Hospital
12:00 pm		
1:30pm	Clinical Photography	
2:00pm		
2:30pm		
3:00pm		
5:00pm		

Thursday 10/13/2016

	APPOINTMENT	LOCATION
8:00		
9:00	Physiatry Evaluation Dr. Paul Occupational Therapy	Rehab Medicine
10:30	Neuropsychology Evaluation	Pick up in 1NW Day Hospital
11:00		
12:30		
1:00		
2:00	Nutrition Consult Jenn Myles	1NW Day Hospital
3:00		
4:00		
5:00		

Friday 10/14/2016

	APPOINTMENT	LOCATION
8:00		
9:00		
10:00	Wrap –Up with Dr Porter Time to be determined	
10:30		
12:00		
12:30		
1:00		
2:00		
3:00		
4:00		
5:00		

Natural History Study in SLOS

Growth Charts for Individuals with Smith–Lemli–Opitz Syndrome

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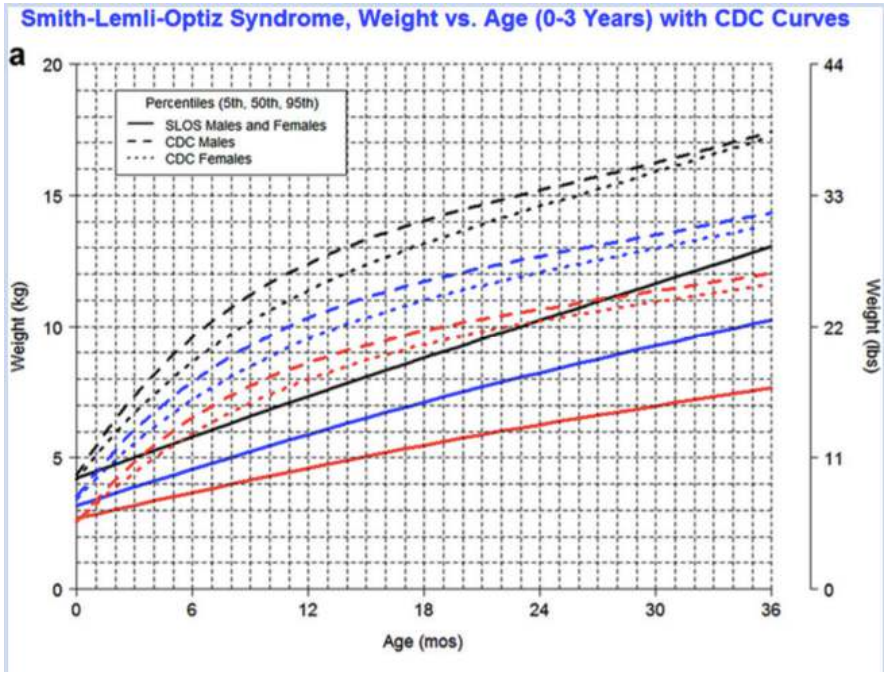

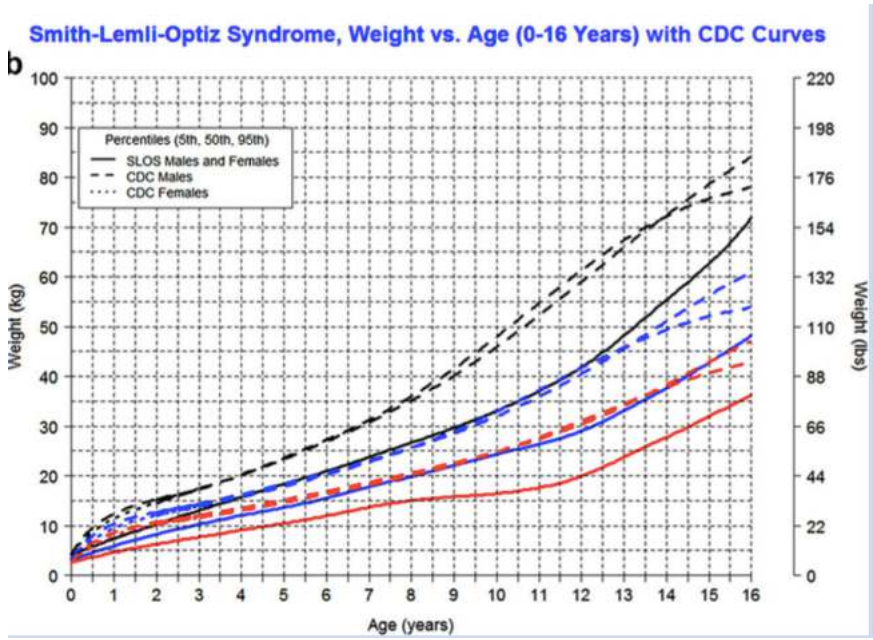

Adrenal Function in Smith–Lemli–Opitz Syndrome

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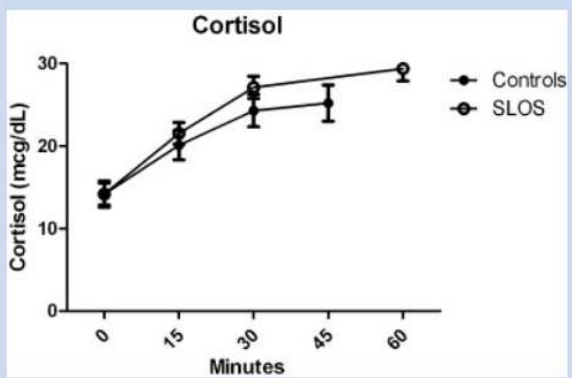

FIG. 2. Area under the curve for cortisol showing baseline value, and timed values. Control cohort represented by filled circles. SLOS cohort represented by hollow circles. Error bar represents standard deviation.

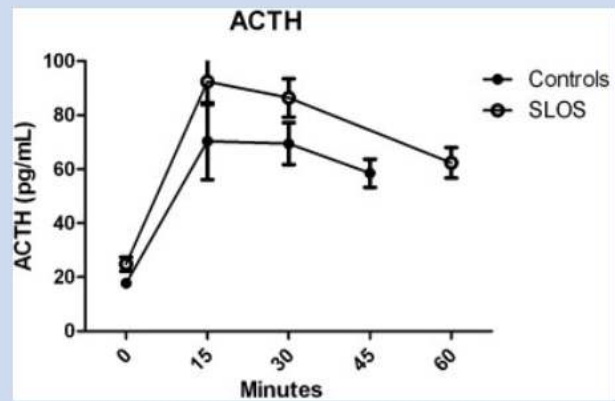

FIG. 1. Area under the curve for ACTH showing baseline value, and timed values. Control cohort represented by filled circles. SLOS cohort represented by hollow circles. Error bar represents standard deviation.

Brain Magnetic Resonance Imaging Findings in Smith–Lemli–Opitz Syndrome

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TABLE II. Brain Anatomical Abnormalities in SLOS Patients (N = 55) Detected by MRI

Abnormality	N	%
Cavum	42	76
Large communicating cavum	21	38
Incomplete corpus callosum	12	22
Hypoplastic or absent rostrum	8	15
Hypoplastic or absent splenium	6	11
Hypoplastic or absent splenium and posterior body	4	7
Thick and/or thin segments of the corpus callosum[a]	31	56
Thick genu	9	16
Thick body	13	24
Thick all segments	2	4
Thin genu	6	11
Thin body	9	16
Thin splenium	15	27
Thin all segments[b]	5	9
Abnormal shape of the corpus callosum[a]	26	47
Foreshortening	13	24
Arching[c]	11	20
Flattening	2	4
Colpocephaly	35	64
Bilateral	21	38
Left only	7	13
Right only	7	13
Minimal[d]	16	15
Mild[d]	30	27
Moderate[d]	8	7
Marked[d]	2	2
Posterior fossa abnormalities	17	31
Mild Dandy–Walker variant	11	20
Cerebellar tonsil ectopia	2	4
Type I Chiari malformation	2	4
Abnormal shape of the cerebellum (not hypoplastic)	1	2
Small glottic cerebellum	1	2
Arachnoid cysts (28 total cysts in 17 patients)	17	31
Midline location, all types[e]	14	50
Quadrigeminal plate cistern[e]	12	43
Middle cranial fossa[e]	7	25
Posterior cranial fossa[e]	5	18
Anterior cranial fossa[e]	2	7
Torcular fossa[e]	1	4
Parietal[e]	1	4
Atrophy	8	15
Diffuse cerebral atrophy	2	4
Central pattern cerebral atrophy	5	9
Generalized cerebellar atrophy	2	4
White matter lesions	2	4

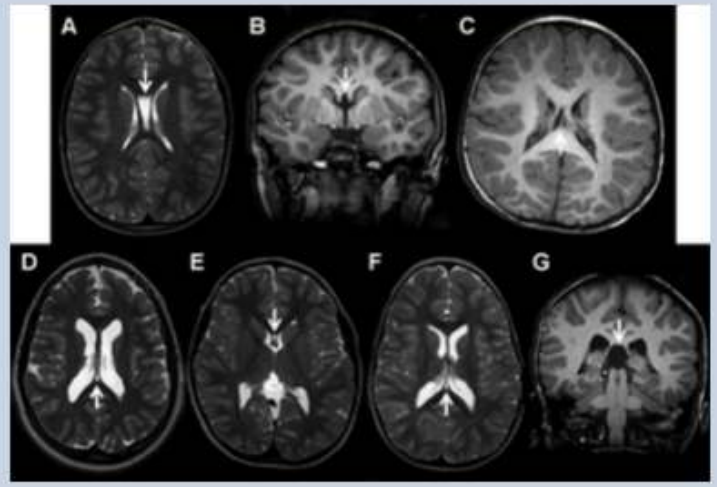

FIG. 1. Septum pellucidum abnormalities. Abnormalities of the septum pellucidum were the most common finding in the SLOS patients. A: Axial and (B) coronal images of a large communicating cavum with dysmorphic septum pellucidum. The cavum is wide and long, and has a discernible communication with the third ventricle; the thickness of each lamina of the divided septum pellucidum is wider than the total thickness of a normal septum pellucidum. This unusual configuration was present in 21 of 55 SLOS patients (38%). Another 21 patients had a more conventional non-communicating cavum, so that a total of 42 patients (76%) had a cavum of some kind. C: One patient with a large communicating cavum and a dysmorphic septum pellucidum also had an anomalous white matter tract crossing the posterior part of the cavum. D: Medium sized non-communicating cavum of the septum pellucidum and cavum Vergae. E: Small non-communicating cavum of the septum pellucidum. F: Medium sized non-communicating cavum Vergae. G: Large cavum of the velum interpositum.

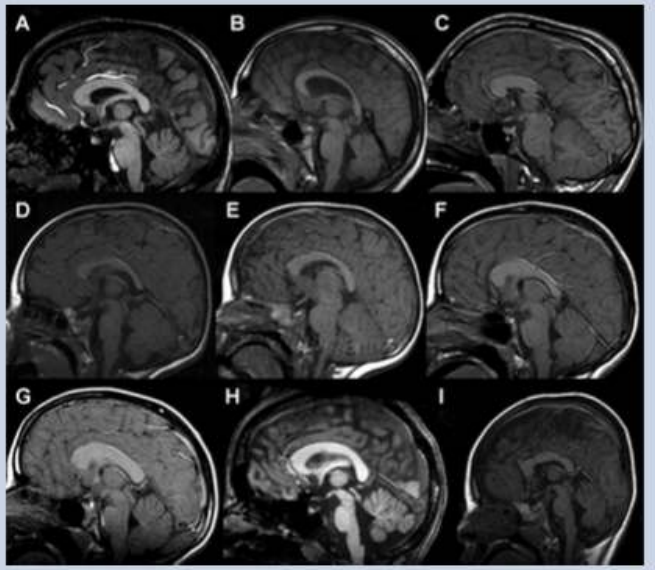

FIG. 2. Corpus callosum abnormalities. Abnormalities of the corpus callosum (CC) were found in 38 SLOS patients (68%). Hypoplastic or absent segments, thick or thin segments, foreshortening, flattening, or excessive arching of the CC were found in a multitude of combinations. A: Normal CC, for comparison. B: The entire CC is thin secondary to enlargement of the third ventricle. C: The splenium and posterior half of the body are absent; the remainder of the CC is unusually thick. D: The entire CC is thin (not secondary to ventricular enlargement) and the arch is flat. E: The splenium is thin, the arch is high, and the length is foreshortened. F: The splenium and posterior body are thin, the anterior body is thick, and the length is foreshortened. G: The whole CC is thick. H: High arch. I: Flat arch, foreshortened.

Decreased cerebral spinal fluid neurotransmitter levels in Smith-Lemli-Opitz syndrome

S. E. Sparks · C. A. Wassif · H. Goodwin · S. K. Conley · D. C. Lanham · L. E. Kratz · K. Hyland · A. Gropman · E. Tierney · F. D. Porter

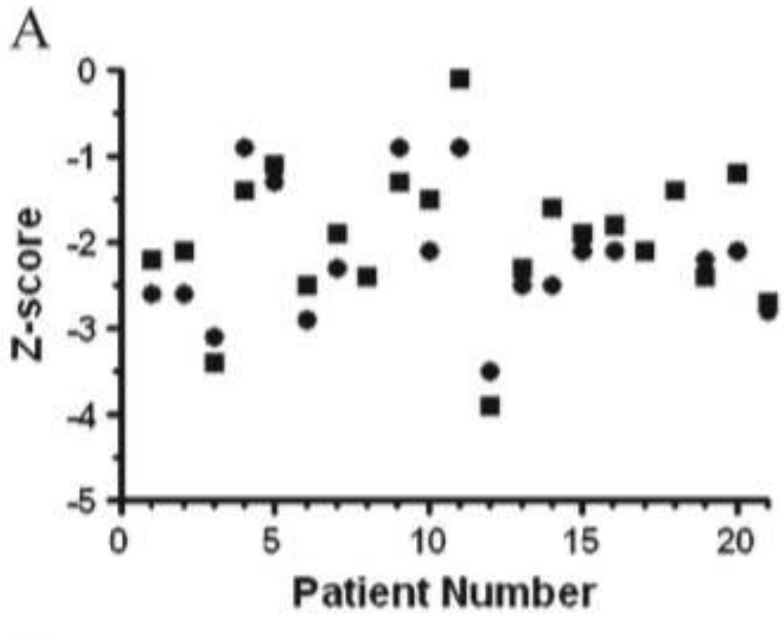

Fig. 1 **a** CSF levels of 5HIAA (*filled squares*) and HVA (*filled circles*) are significantly decreased compared to age appropriate reference ranges. **b** There is a strong correlation (r^2=0.74, p<0.0001) between the degree of 5HIAA and HVA deficiency in individual subjects, suggesting a common underlying mechanism. CSF levels of 5HIAA do not correlate with either CSF cholesterol (**c**) or dehydrocholesterol (**d**) levels

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ORIGINAL ARTICLE

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Vitamin D levels in Smith-Lemli-Opitz syndrome

Miyad Movassaghi[1,2] | Simona Bianconi[2] | Richard Feinn[1] | Christopher A. Wassif[2] | Forbes D. Porter[2]

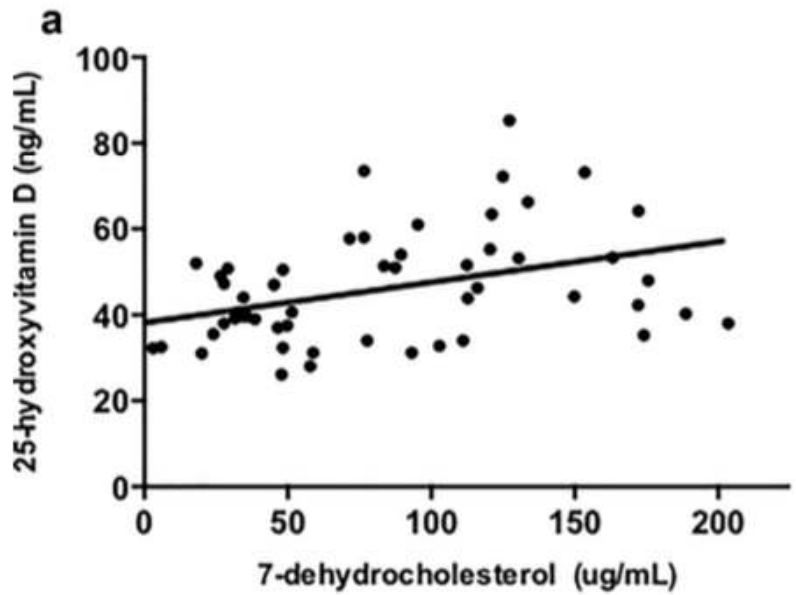


TABLE 2 Vitamin D status: overall and by season (1998–2006) for SLOS and NIH clinical center (NIHCC) patients

Measurements (mean ± SD)	Overall	Winter	Spring	Summer	Fall
SLOS patients 25(OH) D ng/ml (n = 53)	48.06 ± 19.53	42.72 ± 15.75	43.70 ± 17.71	52.70 ± 22.06	50.76 ± 19.42
NIHCC patients (ages 0–18) 25(OH) D ng/ml (n = 867)	30.51 ± 16.142	28.01 ± 15.27	27.69 ± 14.71	33.20 ± 16.51	32.41 ± 17.09

1 nmol/L = 0.40 ng/ml and 1 ng/ml = 2.5 nmol/L.

RESEARCH Open Access

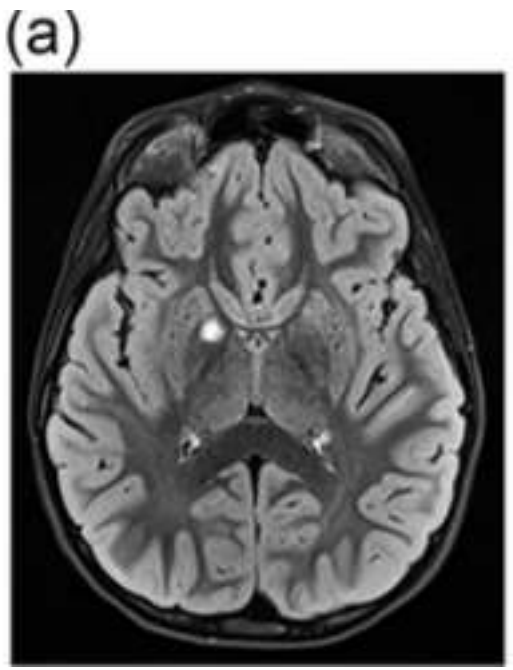
Development, behavior, and biomarker characterization of Smith-Lemli-Opitz syndrome: an update

Audrey Thurm[1], Elaine Tierney[2,4*], Cristan Farmer[1], Phebe Albert[1], Lisa Joseph[1], Susan Swedo[1], Simona Bianconi[3], Irena Bukelis[2], Courtney Wheeler[2], Geeta Sarphare[2], Diane Lanham[2], Christopher A. Wassif[3] and Forbes D. Porter[3]

correlated with Vineland-II or IQ scores. However, serum cholesterol was moderately and positively correlated with Vineland-II and IQ scores, while both serum and CSF DHC levels were moderately and negatively correlated with Vineland-II and IQ. The 7-DHC + 8-DHC to cholesterol ratio in both serum and CSF was significantly and moderately-to-strongly related to all Vineland-II and IQ variables, and serum was significantly correlated with anatomical severity score. None of the markers were significantly

Spontaneously regressing brain lesions in Smith–Lemli–Opitz syndrome

An N. Dang Do[1] | Eva H. Baker[2] | Katherine E. Warren[3] | Simona E. Bianconi[1] | Forbes D. Porter[1]



doi: 1

Letter to the Editor

Pregnancy in an individual with mild Smith–Lemli–Opitz syndrome

Discordant Phenotype and Sterol Biochemistry in Smith–Lemli–Opitz Syndrome

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