



We Treat Kids Better



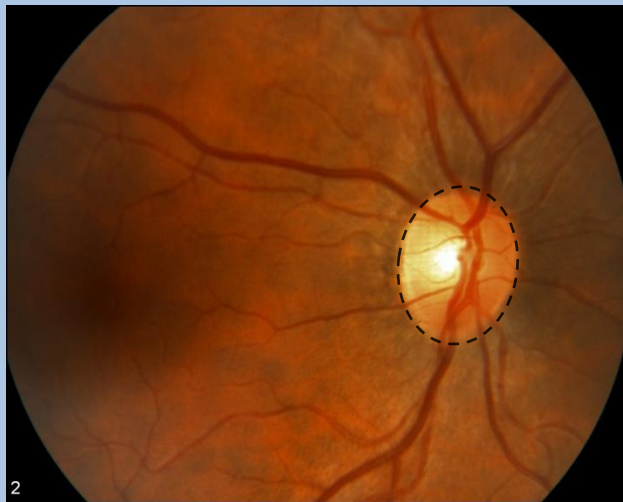
Reconsidering Septo-Optic Dysplasia

Mark Borchert, MD

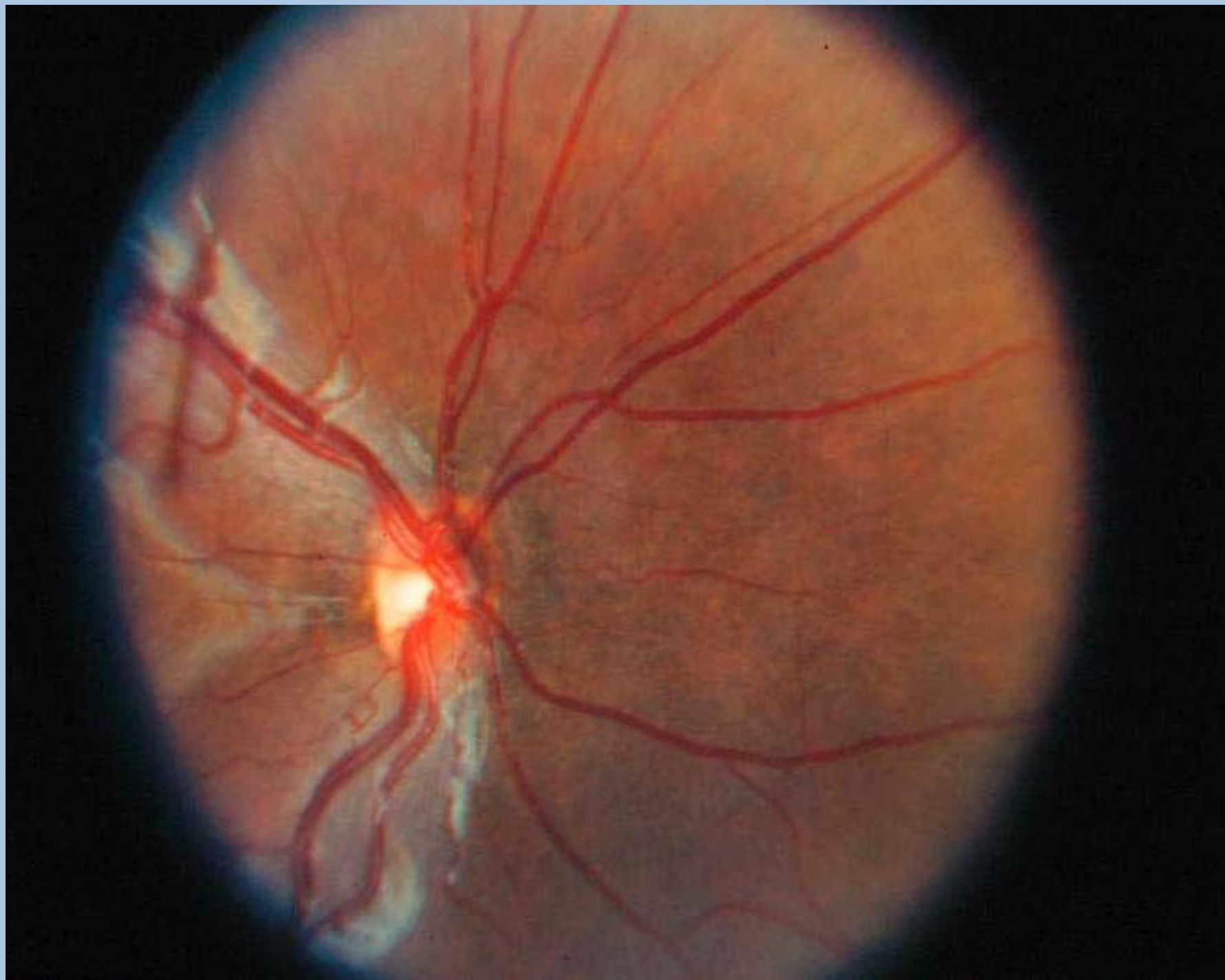
- How is ONH diagnosed?
- What is “septo-optic dysplasia?”
- What are the medical and developmental consequences of ONH?

Optic Nerve Hypoplasia

Definition: Underdeveloped optic nerve in one or both eyes



Birth defect estimated to occur between 7th & 15th gestational week

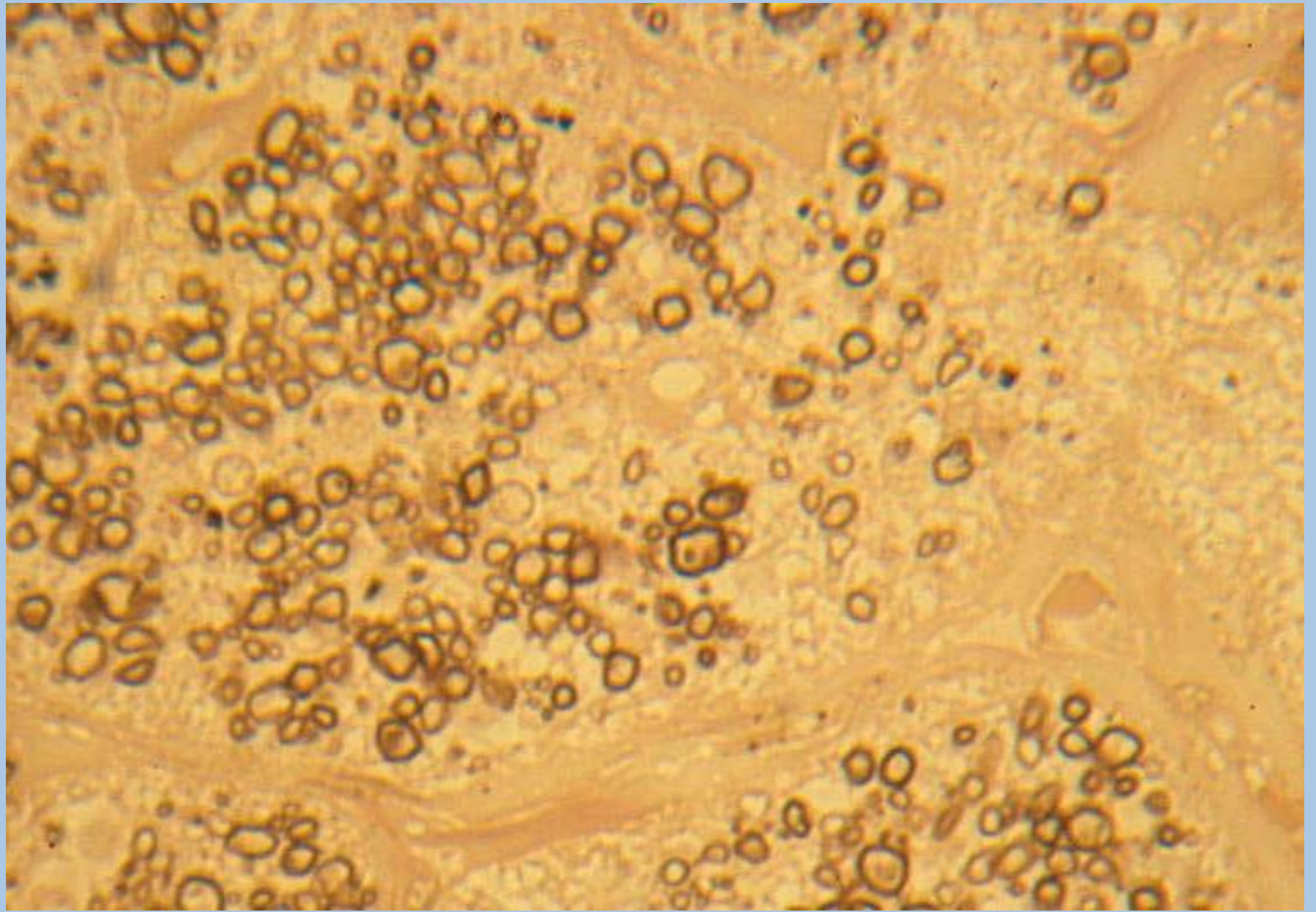


Optic Nerve Development

- 7th week: axons extend down optic stalk
- 11th week: axons reach LGN
- 16th week: 3.5 million axons in nerve
- 40th week: 1.2 million axons in nerve

Pathogenesis of ONH

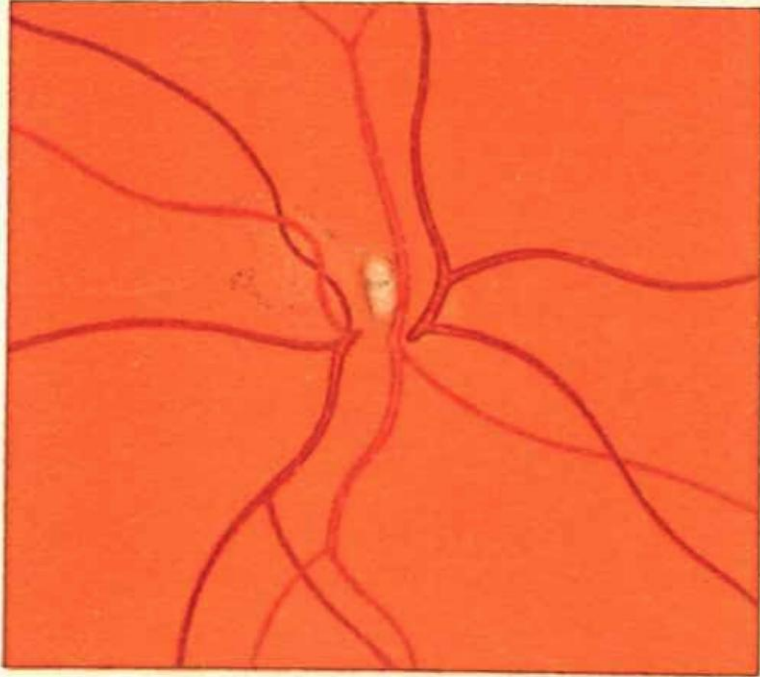
- Nerve fibers fail to reach target destination
and /or
- Fibers undergo excessive apoptosis



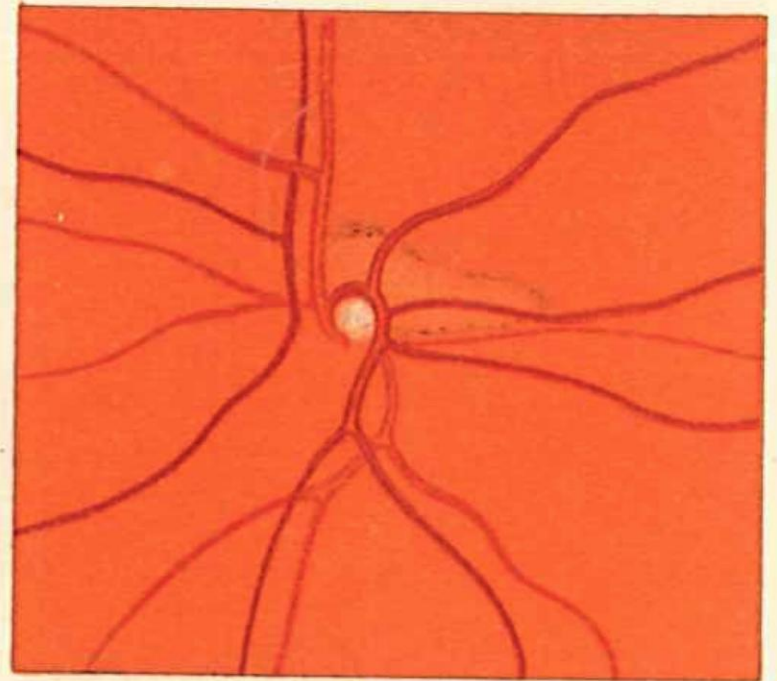
History of ONH in Literature

Magnus K: Clin Monatsbl Augenh 1884, 32:85

Schwarz O: Ein Fall von mangelhafter Bildung beider Sehnerven. Albrecht von Graefes Arch Klin Ophthalmol 1915, 90:326



*Rechtes Auge.
(aufrechtes Bild)*



*Linkes Auge.
(aufrechtes Bild)*

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Reeves D: Congenital absence of the septum pellucidum. Bull Johns Hopkins 1941, 69:61–71.

CONGENITAL ABSENCE OF THE SEPTUM PELLUCIDUM
A CASE DIAGNOSED ENCEPHALOGRAPHICALLY AND ASSOCIATED WITH
CONGENITAL AMAUROSIS

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(Neurological) of the University of Southern California*

Submitted for publication April 23, 1941

According to Dolgopol (1), only four cases of absence of the septum pellucidum in fully developed brains, and two in fetal brains have been reported. The first of these was that of Tenchini (2) in 1880, and the second that of Hochstetter (3) in 1925. Prior to this, Hochstetter had observed absence of the septum pellucidum in otherwise well-formed brains of fetuses about the third and fifth month of gestation. He believed congenital absence of the septum pellucidum was not rare and usually escaped attention. In 1930 Hahn and Kuhlenbeck (4) also discovered the anomaly in the dissecting room, but no information on the history of the patient was obtained. Dolgopol added an additional case discovered at autopsy in 1938.

In 1935 Dyke and Davidoff (5) demonstrated this anomaly encephalographically for the first time in a 23 year old woman with post-encephalitic disorders of behavior. Undoubtedly Dandy's (6) description of the pneumographic picture of congenital cerebral cysts of the cavum septi pellucidi and cavum vergae in 1931, and those by Davidoff and Dyke (7) and Hyndman and Penfield (8) of absence of the corpus callosum led to a more easily appreciated picture of absence of the septum pellucidum. Sfintzescu and Mihailescu (9) reported a case found ventriculographically in 1936, and although others may have been overlooked, those diagnosed pneumoencephalographically have at all events been extremely uncommon, and for that reason as well as for the fact that the present case is the youngest so diagnosed, it was believed worthy of publication.

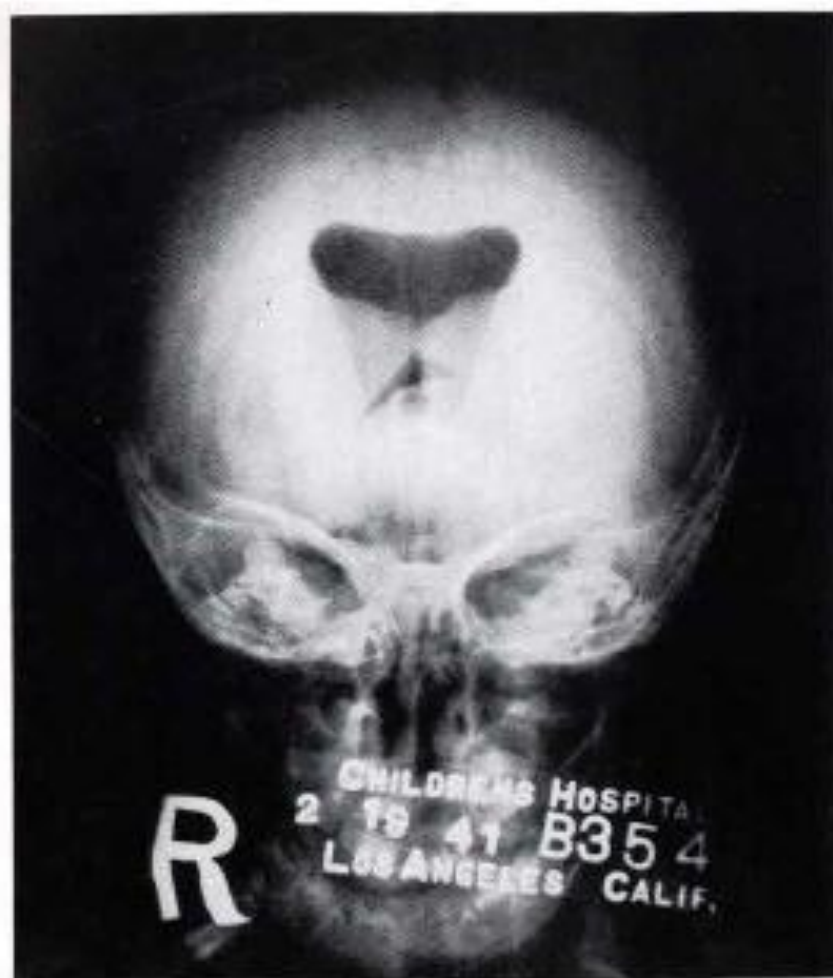


FIG. 2. ENCEPHALOGRAM. ANTEROPOSTERIOR VIEW SHOWING MEDIAL CONFLUENCE OF THE LATERAL VENTRICLES ANTERIORLY RESULTING FROM ABSENCE OF THE SEPTUM PELLUCIDUM

normal. In the neurological examination, the optic discs were seen only with difficulty and appeared to be pale. Subsequent examination by Dr. Rodman Irvine under ether anesthesia led him to the diagnosis of bilateral primary optic atrophy of undetermined origin, probably, however, on the basis of a congenital aplasia. The pupils failed to react to light and there was no blinking of the eyes when objects were brought suddenly toward them. There was a strabismus and

20. III. Agénésie du septum lucidum avec malformation du tractus optique. La dysplasie septo-optique

Par G. DE MORSIER (Genève)

L'agénésie du septum lucidum paraît être aussi rare que celles du c. calleux, des lobes olfactifs et du vermis que nous avons étudiées précédemment¹⁾. Nous n'avons trouvé que 11 cas anatomo-cliniques publiés avant le nôtre et 23 cas diagnostiqués par l'encéphalographie gazeuse. Généralement l'examen anatomique du cerveau, fait uniquement à l'œil nu, est très sommaire. Aucun cas n'a été examiné sur coupes microscopiques.

Voici le résumé des cas comportant un examen anatomique du cerveau:

1. *Teschini*, 1880. – Demetrio B., âgé de 2 ans $\frac{1}{2}$, mort le 8 novembre 1883 d'une méningite purulente. L'enfant était *très intelligent et gentil*, il ne présentait aucune malformation corporelle. Examen du cerveau à l'Institut d'Anatomie de Pavie. Poids: 923 g. Le cerveau est bien conformé extérieurement. Sur une coupe transversale on remarque l'absence complète du septum lucidum. Ventricule unique: l'épendyme passe d'un ventricule à l'autre sans interruption. La voûte à quatre piliers (fornix) est normalement développée dans chacune de ses parties mais n'adhère pas au c. calleux. La commissure grise manque. Pas d'autres anomalies.

2. *Gibson*, 1924. – Homme d'âge moyen, ayant passé ses dernières années dans un hospice pour aliénés incurables. Six ans avant sa mort, il a été blessé à la tête par la pointe d'un pic qui est entrée profondément dans la région pariétale du crâne et a pénétré jusqu'à la région frontale antérieure, près de la fissure sagittale. Pas d'examen clinique. Cerveau: le septum lucidum existe, il a deux fois sa longueur normale et il est percé d'un grand nombre d'orifices de toutes dimensions. La cavité du septum est oblitérée. *Le fornix est déplacé en avant et en bas*; il est peu développé. Le c. calleux est plus grand que normalement, sauf à un endroit où il est très aminci et mal formé. Les deux ventricules latéraux communiquent largement par les orifices. Ils sont un peu dilatés. Il semble y avoir corrélation entre cet élargissement et les autres malformations.

¹⁾ *Morsier, G. de*: Etudes sur les dysraphies crânio-encéphaliques: I. Agénésie des lobes olfactifs (télencéphalosechisis latéral) et des commissures calleuses et antérieures (télencéphalosechisis médian). La dysplasie olfacto-génitale. Arch. Suisses Neurol. Psychiat., 1955, 74, 309-361.

Morsier, G. de: Etudes sur les dysraphies crânio-encéphaliques: II. Agénésie du vermis cérébelleux. Dysraphie rhombocéphalique médiane (rhomboschisis). Mchr. Psychiat. Neurol. 1955, 129, 321-344.

Georges deMorsier

Geneva 1894-1982

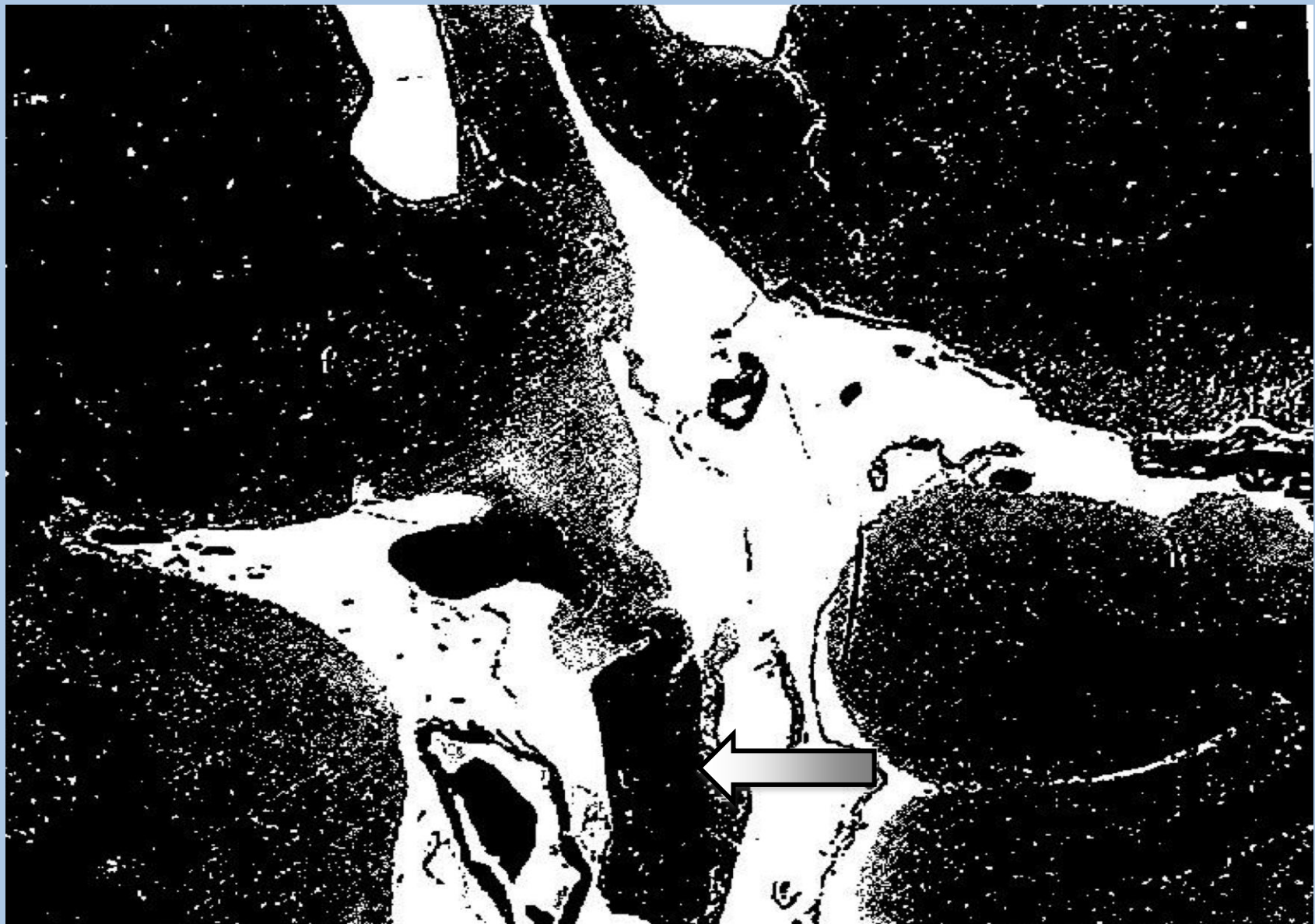


Courtesy of Prof. Avi Safran

“Septo-optic dysplasia”

DeMorsier (1956):

- 84 y/o woman without known vision problems died from complications of pyelonephritis
- Absent septum pellucidum, thin corpus callosum, vertically rotated left optic tract



“Septo-optic dysplasia”

DeMorsier (1956):

- 44 y/o man with absent septum pellucidum on air encephalogram
- “enlargement of the blind spot”

“Septo-optic dysplasia”

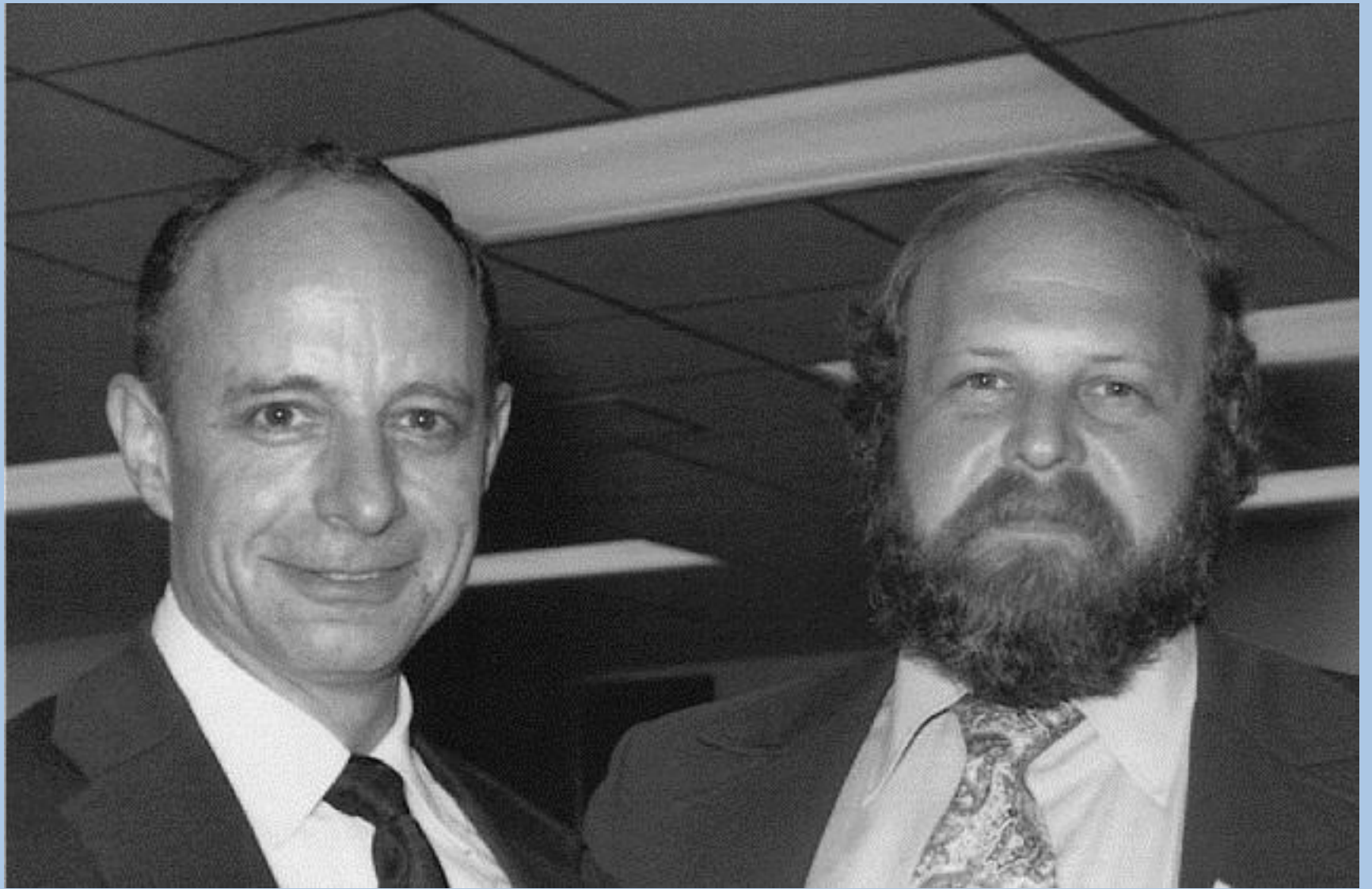
DeMorsier (1956):

- 34 literature cases with absent septum
 - 11 autopsy; 23 encephalographic
- 8 with eye findings:
 - Bilateral anophthalmos 1
 - Bilateral optic atrophy 3
 - Unilateral optic atrophy 3
 - ONH (Reeves) 1

History of ONH in Literature

Gross & Hoff (1959):

- 465 brains with severe neurologic impairment
- 13 with absent septum pellucidum
 - One with bilateral ONH



History of ONH in Literature

- Hoyt, et.al. (Lancet, 1970):

Nine cases of ONH and pituitary dwarfism

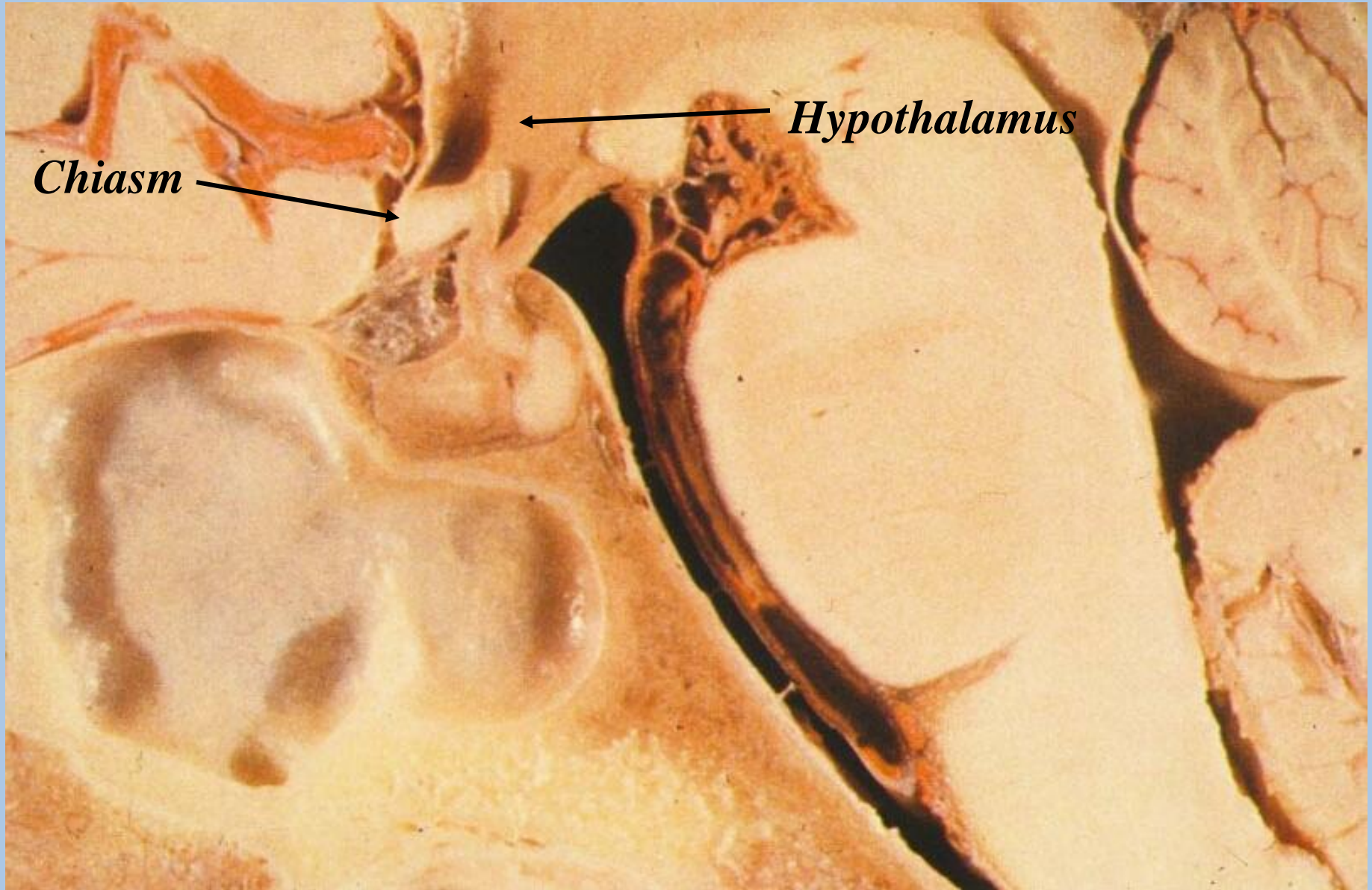
Four missing septum pellucidum

Resurrected “septo-optic dysplasia”

- Ellenberger & Runyan (1970):

One case of ONH and pituitary dwarfism

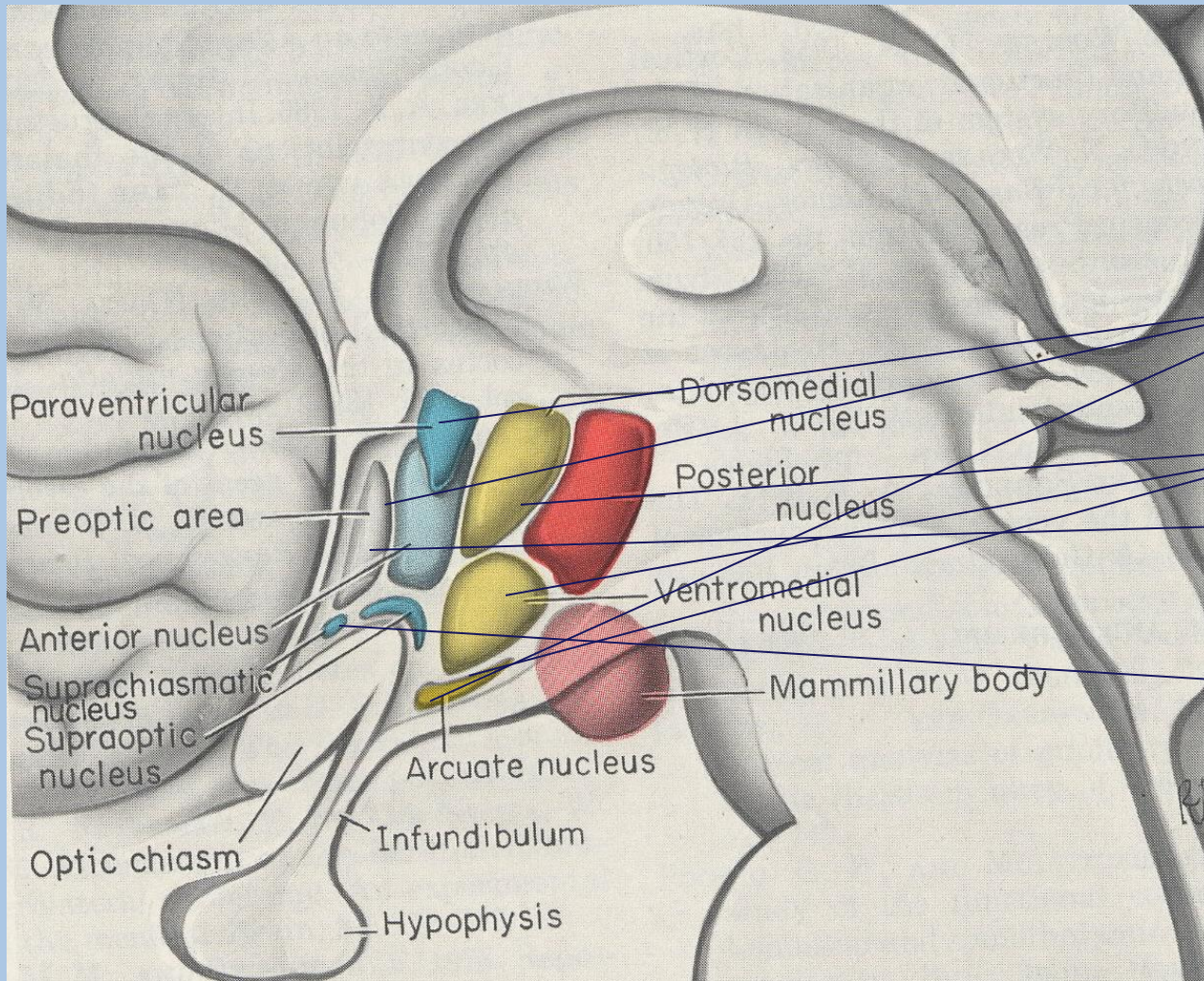
Absent septum pellucidum predicted by Hoyt



Chiasm

Hypothalamus

Hypothalamus



• pituitary hormones

• hunger

• temperature

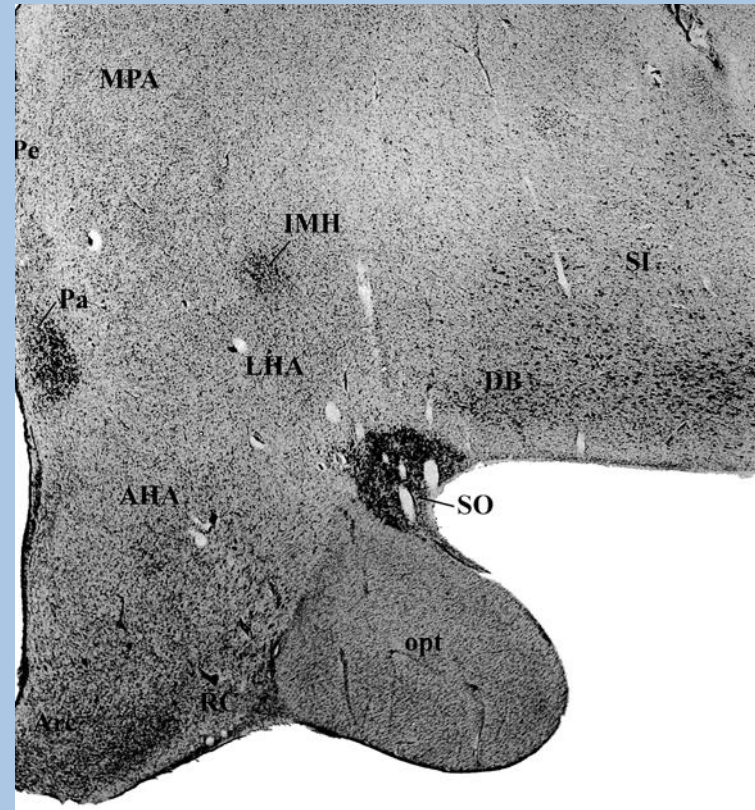
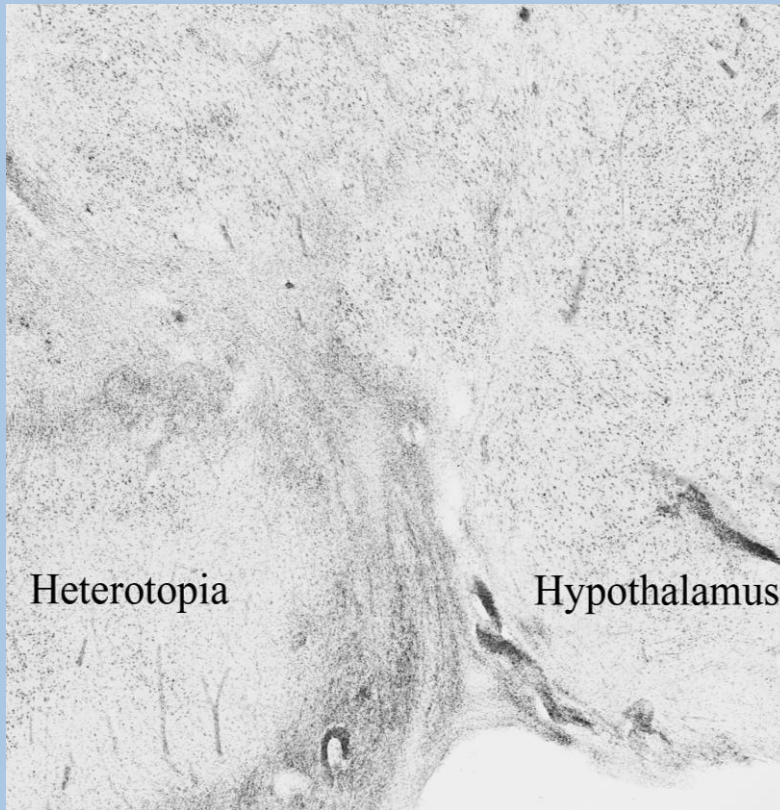
• thirst

• sleep

Hypothalamus

ONH

Normal



Signs of Hypothalamic Dysfunction

- Hypopituitarism
- Food or water seeking
- Obsessive-compulsive behavior
- Obesity
- Abnormal temperature regulation
- Circadian disorders

Hypopituitarism

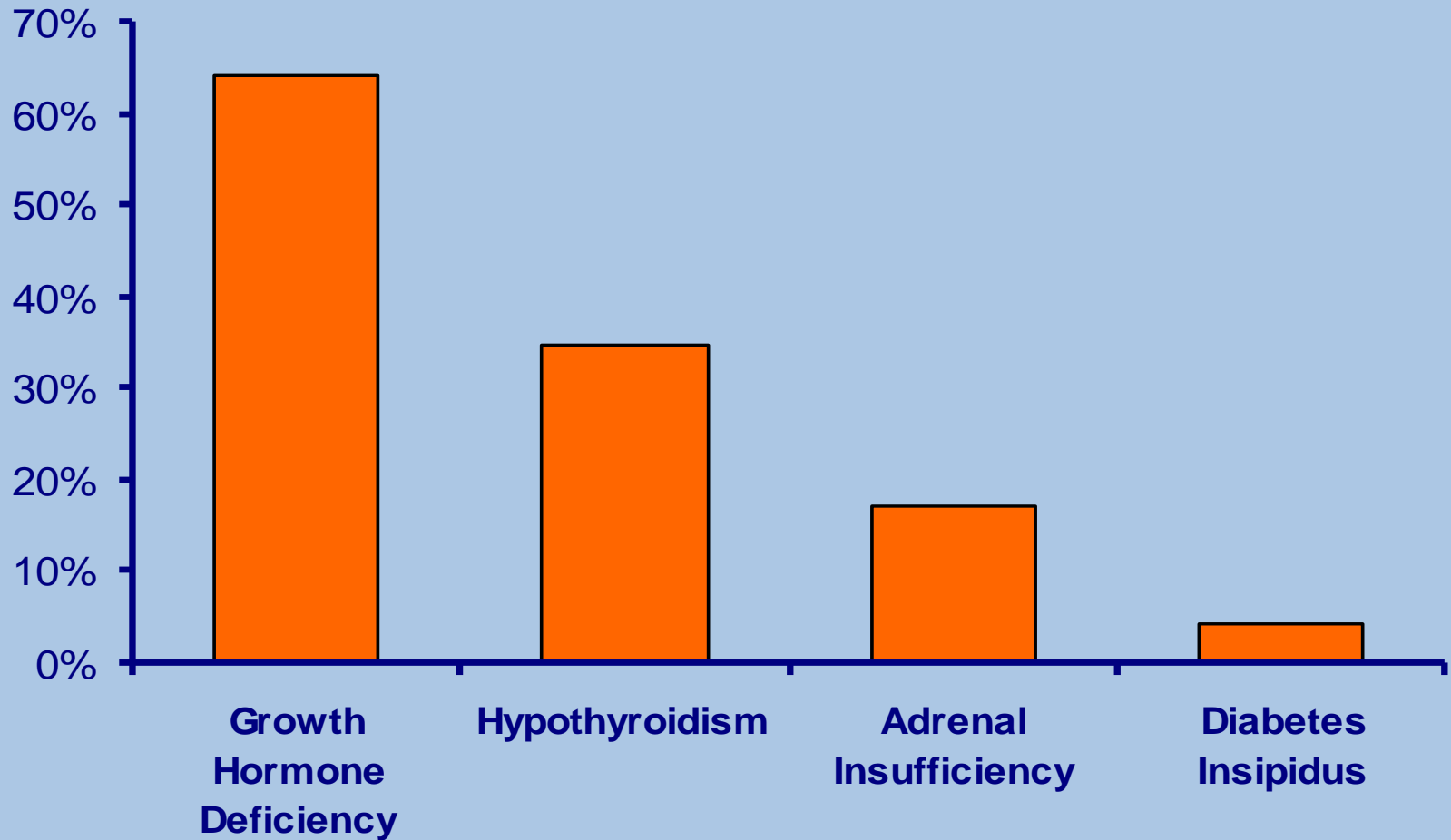
- Deficiencies in:
 - Growth hormone
 - Thyroid hormone
 - ACTH (cortisol)
 - Anti-diuretic hormone (diabetes insipidus)
 - Sex hormones

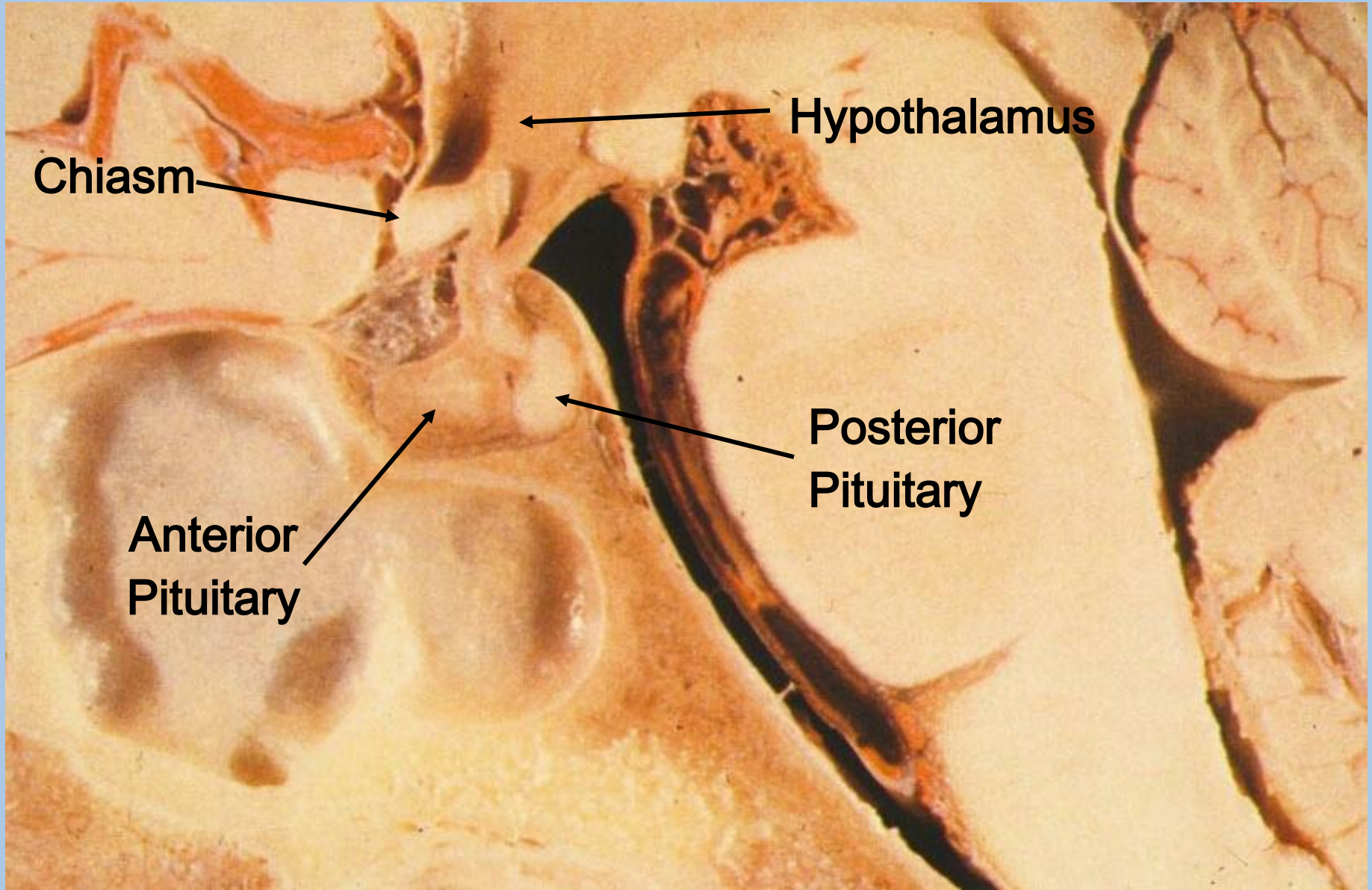
CHLA Prospective ONH Study

Children ≤ 2 yrs. followed until adolescence

- ✓ Identify clinical risk factors for poor outcomes
 - Developmental
 - Endocrinologic
 - Vision
- ✓ Identify prenatal risk factors for ONH

Frequency of Pituitary Hormone Deficiencies in Children with ONH



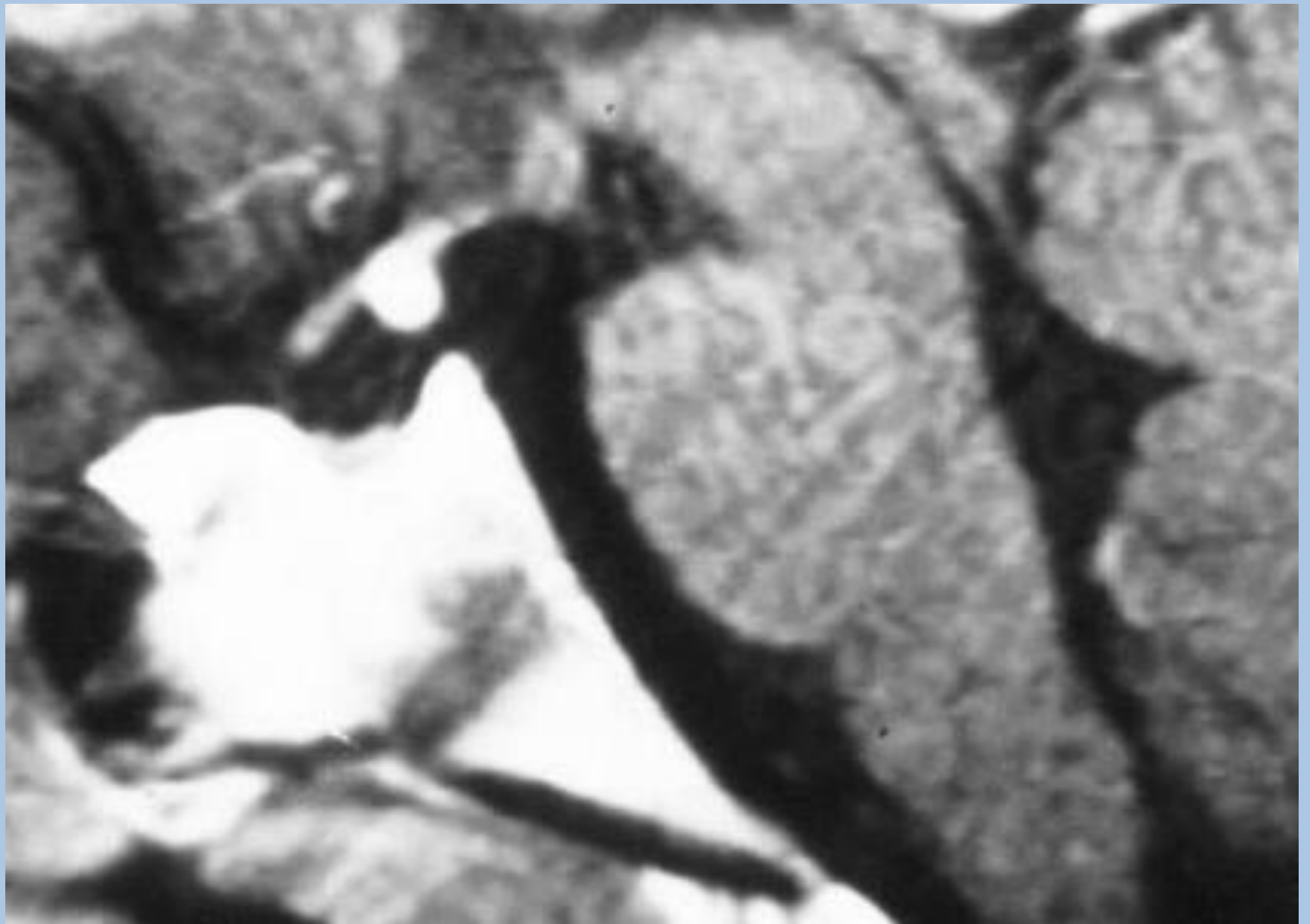


Chiasm

Hypothalamus

**Anterior
Pituitary**

**Posterior
Pituitary**



MRI Pituitary Abnormality

- 13% of ONH patients have pituitary abnormalities
 - 100% have endocrine deficiency
- 87% have no pituitary abnormalities
 - 71% have endocrine deficiency

Objectives: To report our experience with sudden death in children with septo-optic dysplasia and to identify specific risk factors and suggest preventive measures to minimize mortality.

Methods: Clinical data from 5 children with septo-optic dysplasia who died suddenly and unexpectedly were evaluated retrospectively.

Results: All children had corticotropin deficiency, all had thermoregulatory disturbances, and 4 children had diabetes insipidus. In at least 4 children, clinical dete-

rioration was caused by fever and dehydration from a presumed viral illness, which appeared to precipitate adrenal crisis.

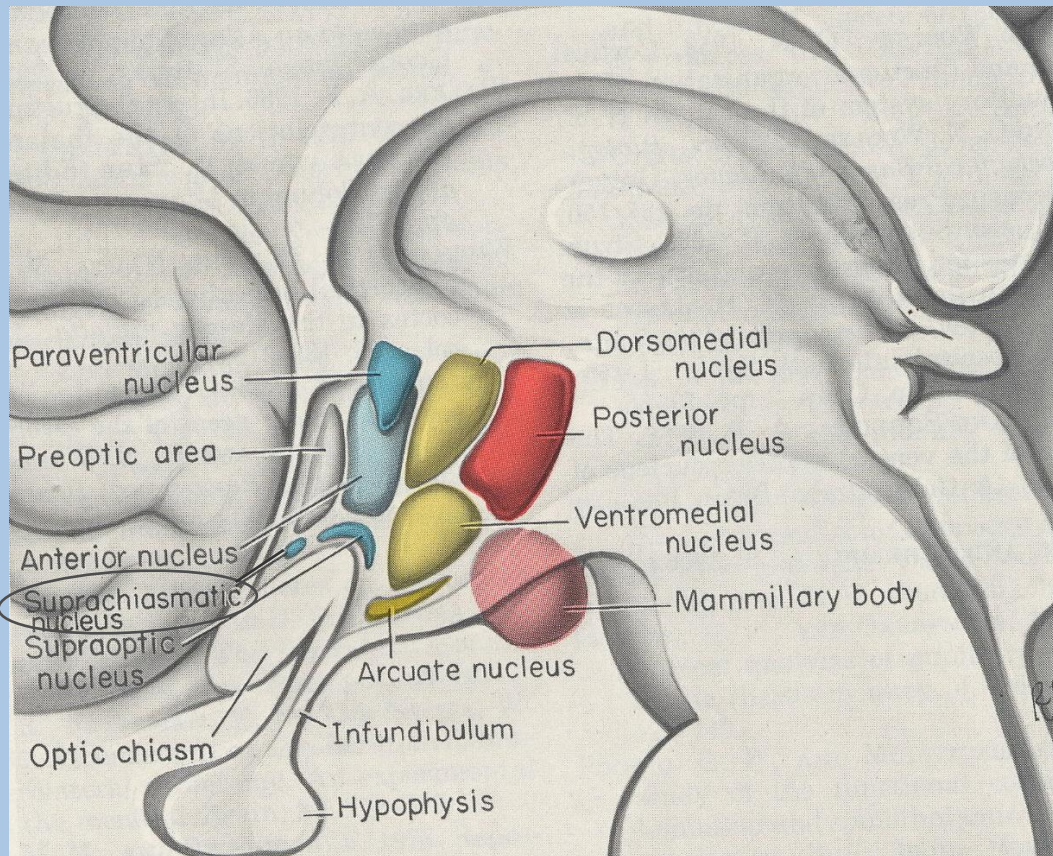
Conclusions: Children with septo-optic dysplasia and hypocortisolism are at risk for sudden death during febrile illness. Thermoregulatory disturbances and dehydration from diabetes insipidus may potentiate clinical deterioration. Prevention of sudden death in septo-optic dysplasia requires early recognition and treatment of these major risk factors.

Arch Ophthalmol. 1997;115:66-70

THE TERM *septo-optic dysplasia* denotes the association of optic nerve hypoplasia with an absent septum pellucidum and a thin corpus callosum, a condition first recognized in neuropathological specimens by de Morsier in 1956.¹ The clinical association of septo-optic dysplasia with pituitary hormone de-

evaluated serum liver enzymes shortly after birth. She was hospitalized during the first week of life and treated with antibiotics for possible sepsis despite negative blood cultures. Bilateral optic nerve hypoplasia was diagnosed when she was 1 month old. At 18 months of age, an endocrinologic evaluation disclosed panhypopituitarism and she was given exogenous hormone

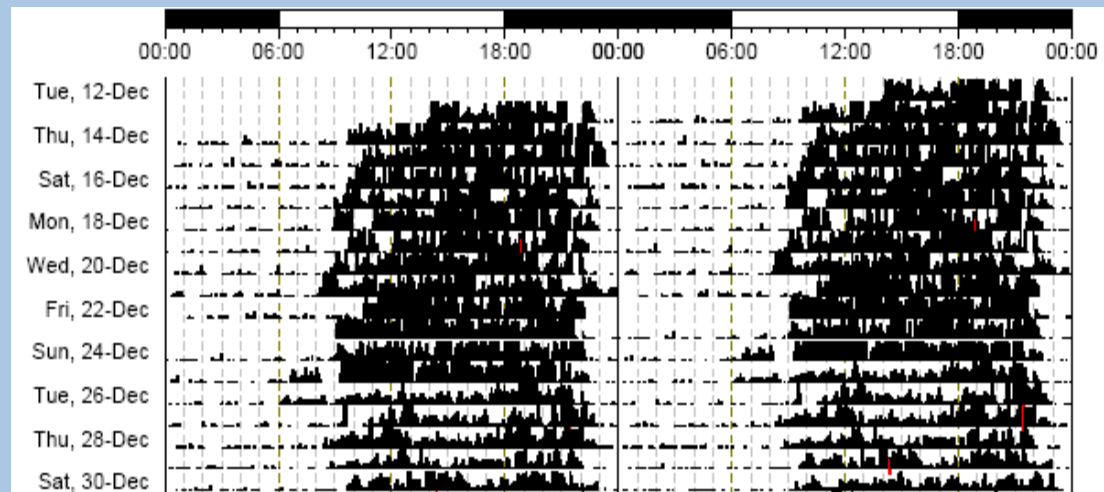
Hypothalamus & Sleep Regulation



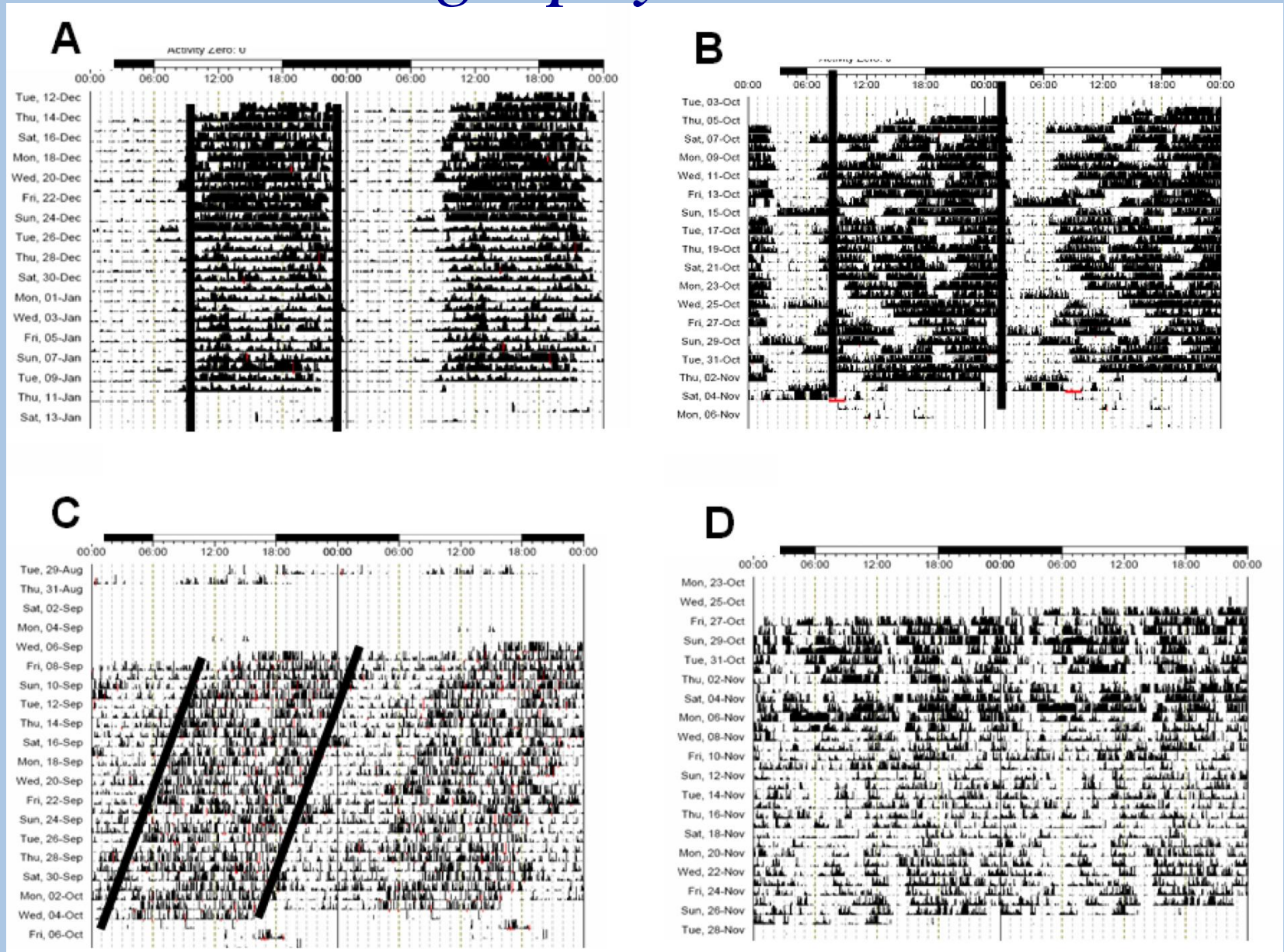
Suprachiasmatic Nucleus:

- Located in hypothalamus
- Controls circadian rhythms

Actigraphy

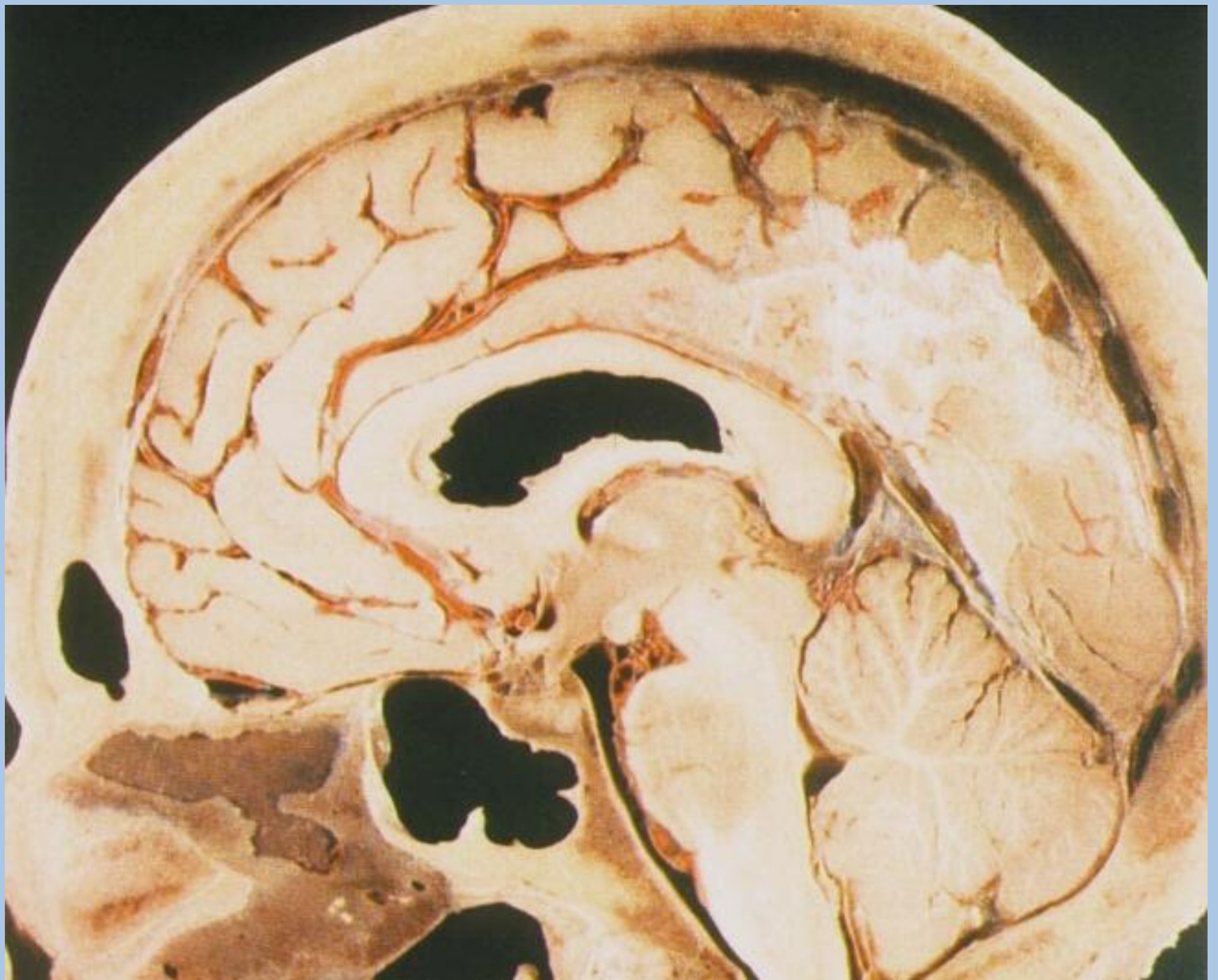


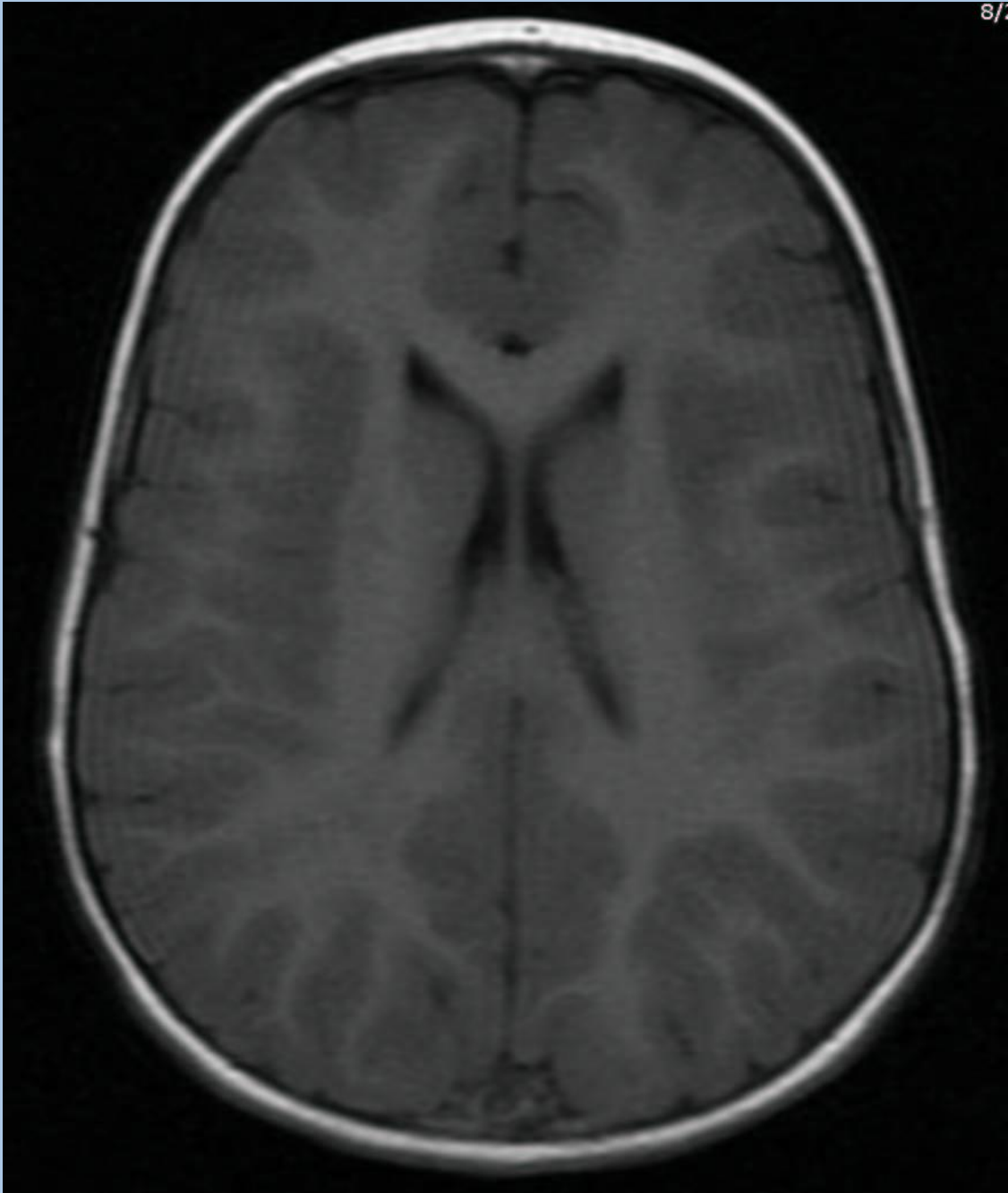
Actigraphy in ONH

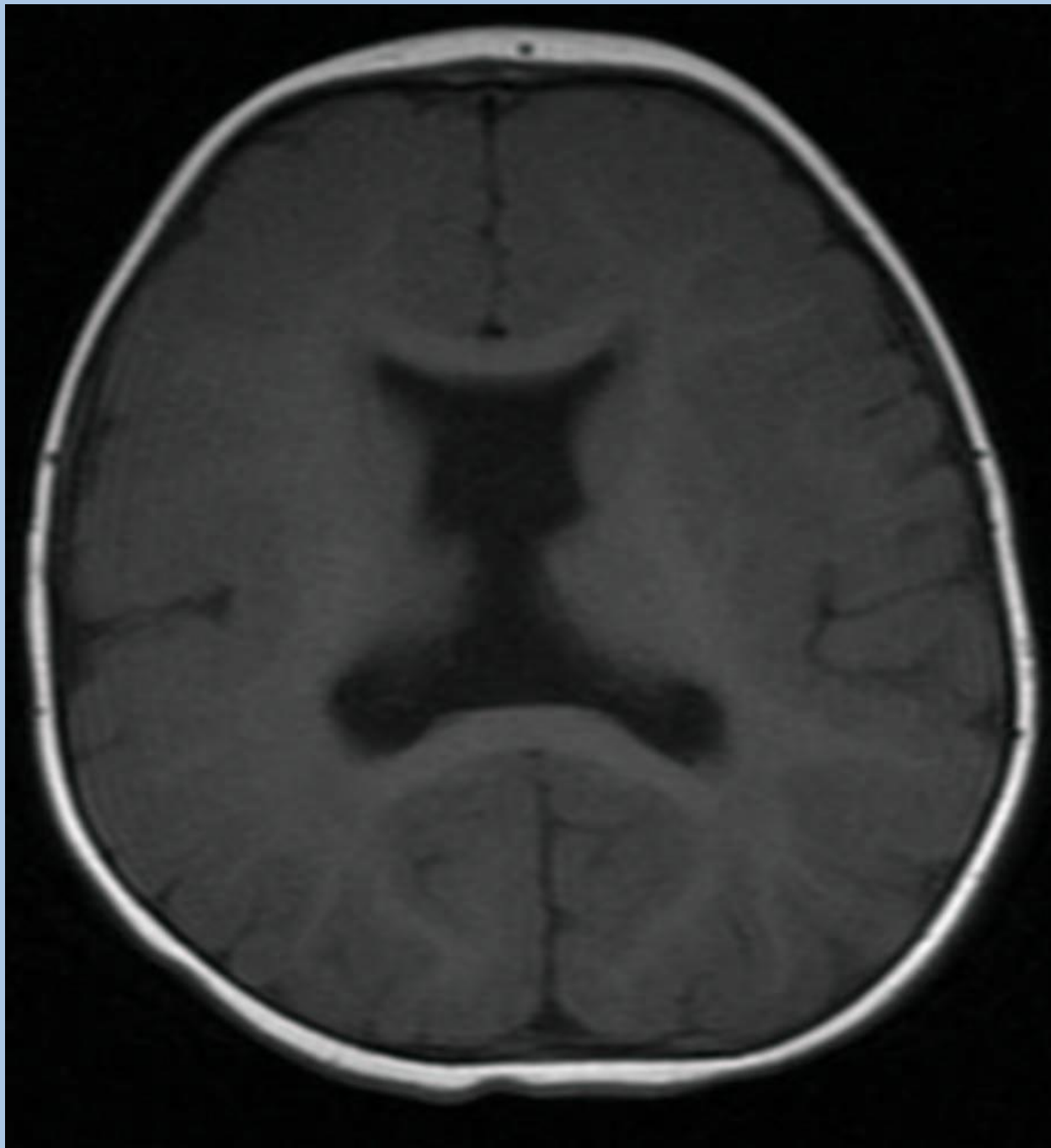


Circadian Dysfunction

- 30% of ONH patients have abnormal rest activity
- Disruptive to family
- Abnormal rest-activity correlates:
 - Worse vision
 - ≥ 3 hormone deficits
 - Severe developmental delay





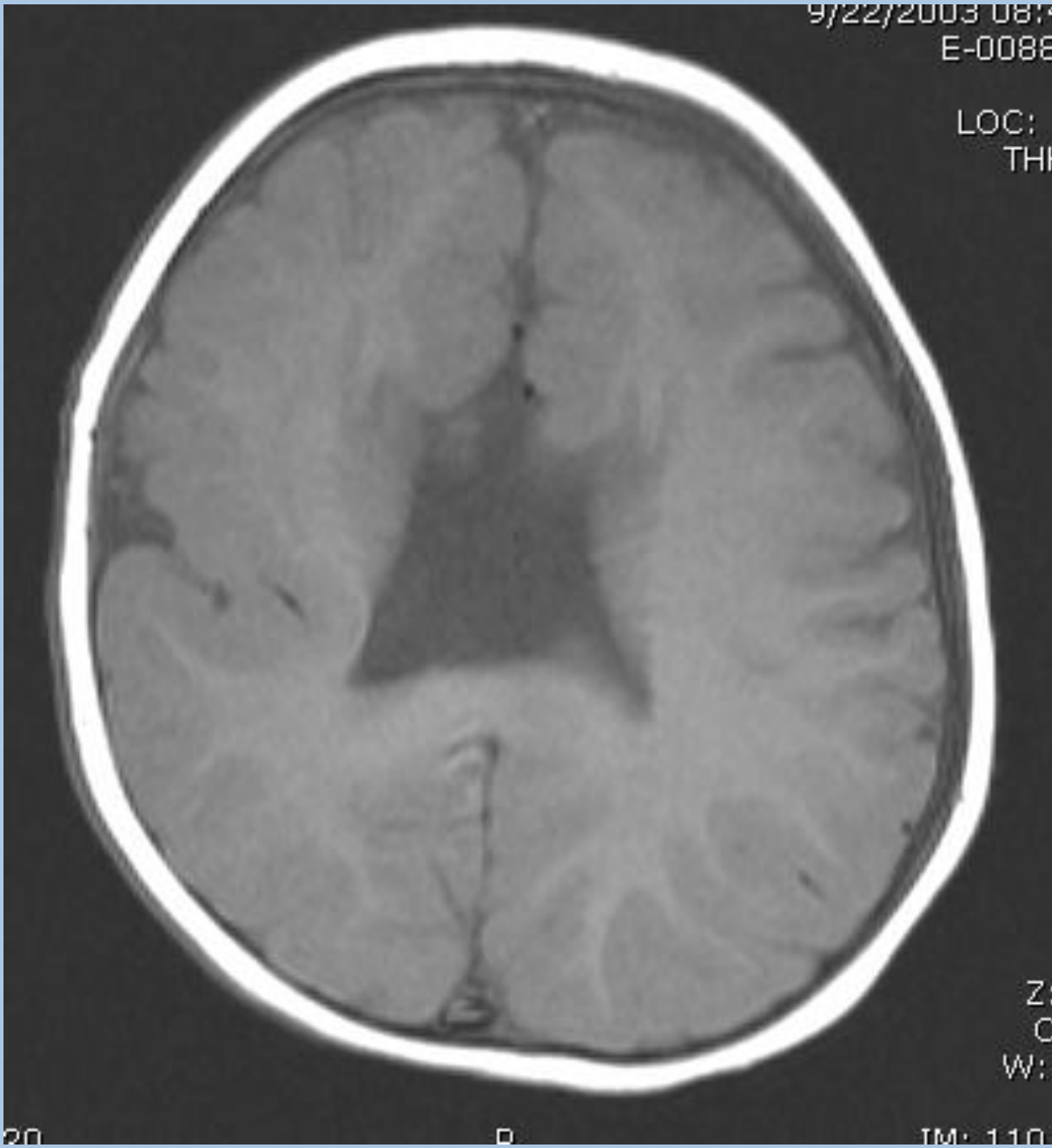


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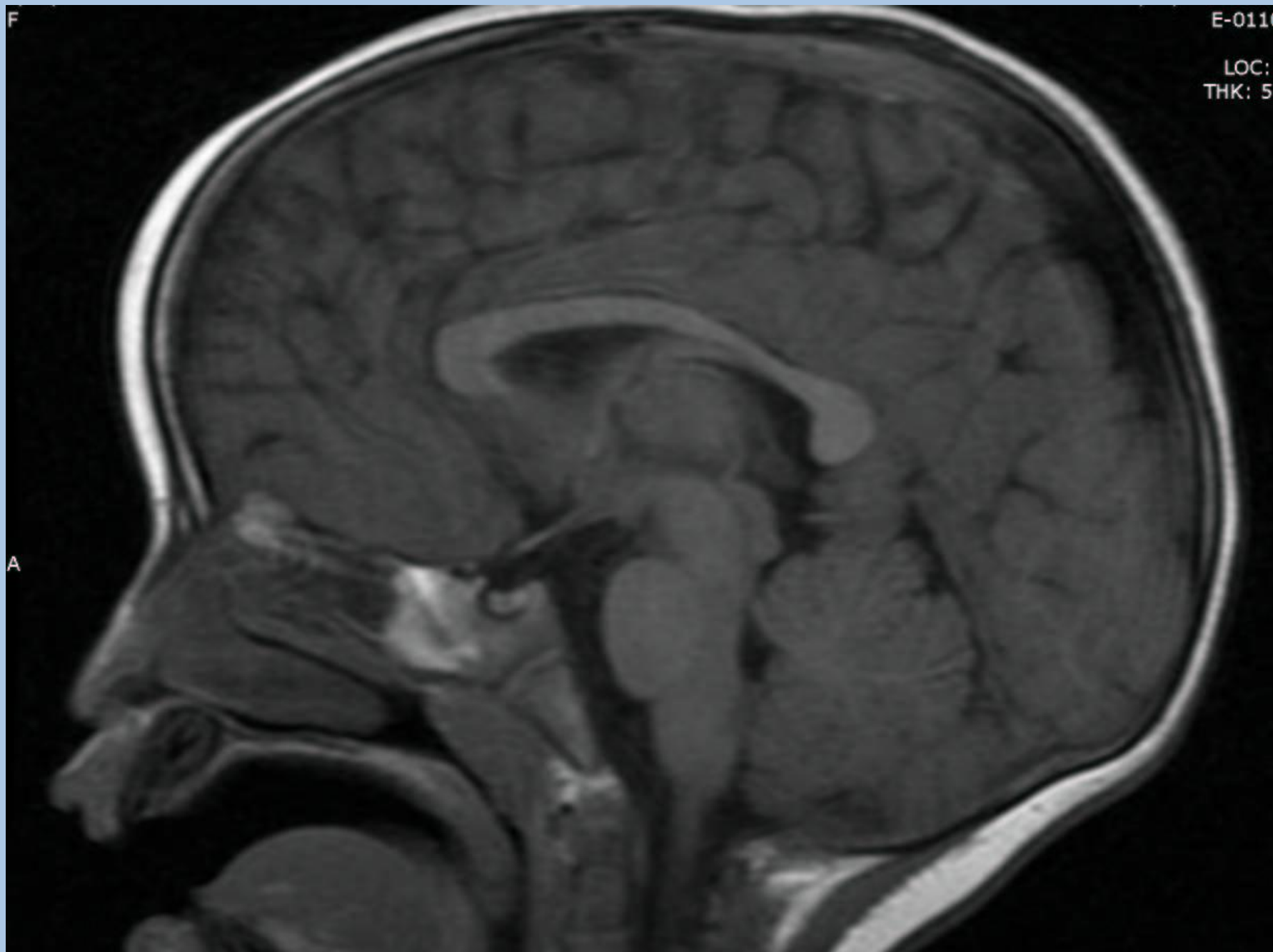
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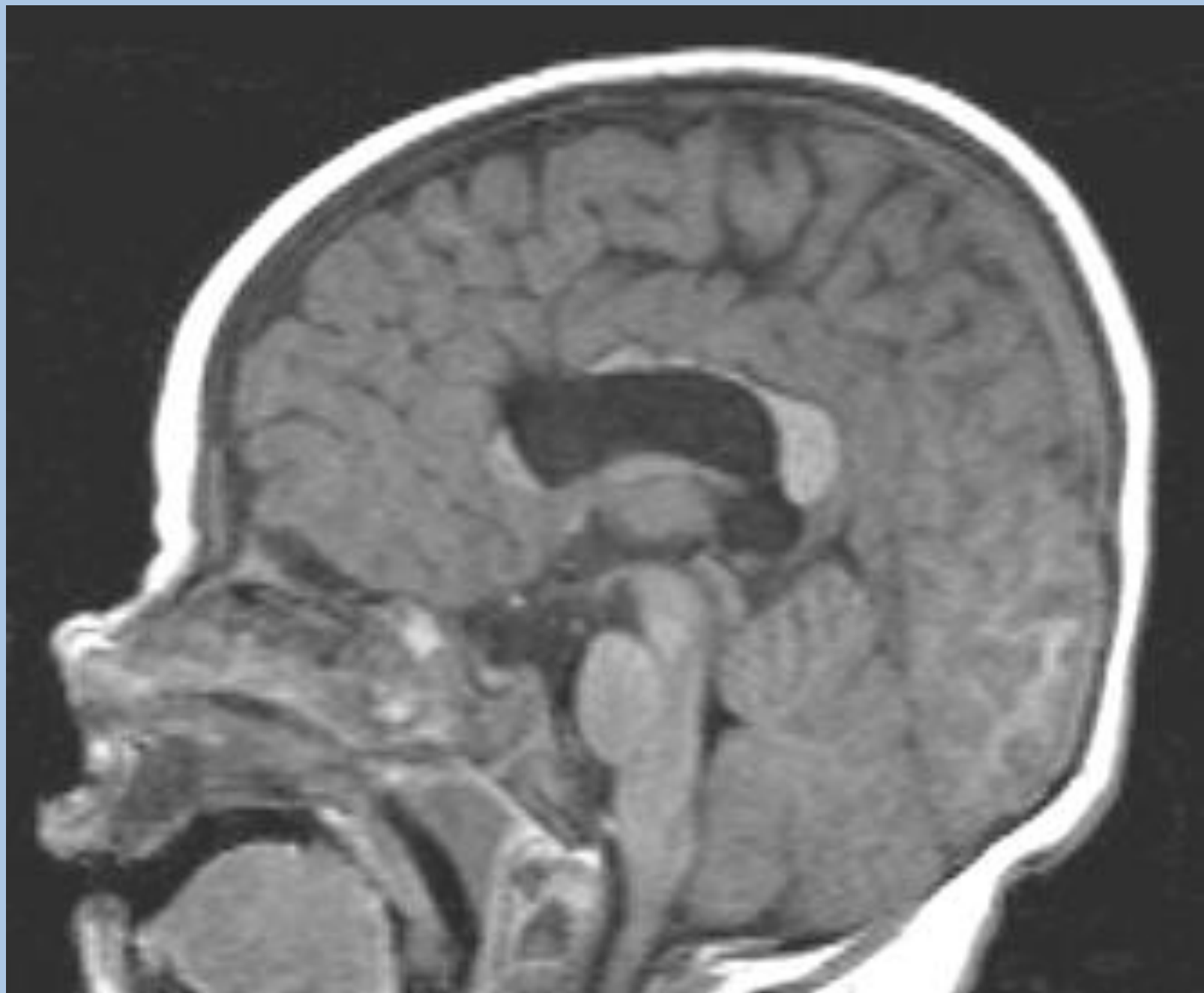
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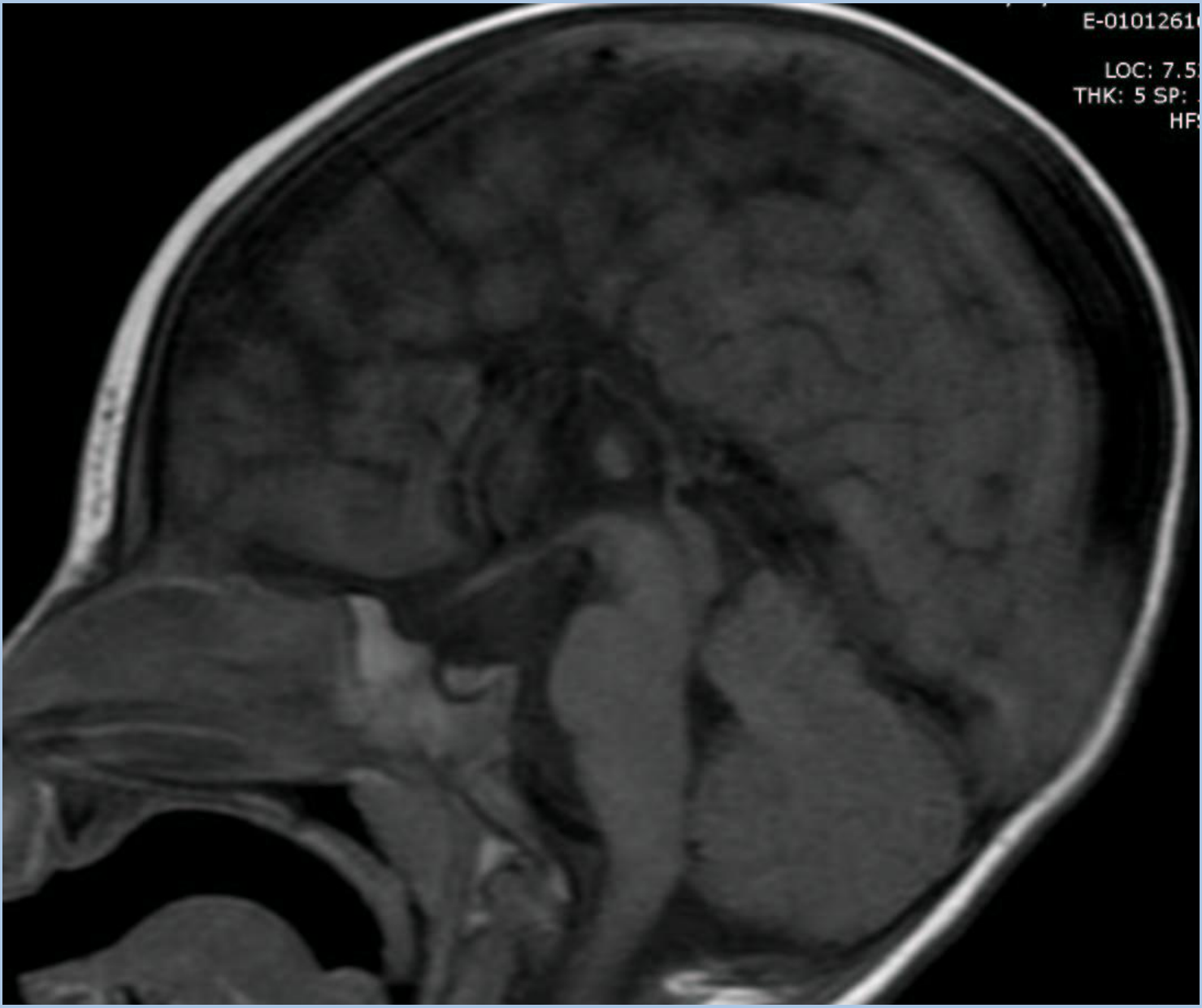
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CNS Abnormalities in ONH

- Hypoplasia of corpus callosum 42%
- Absence of septum pellucidum 38%
- Pituitary dysgenesis 13%
- Other major malformations 14%
 - hydrocephalus
 - white matter hypoplasia
 - cortical heterotopias
 - micropolygyria
 - schizencephaly

MRI Findings & Developmental Delay

- Septum Pellucidum
 - 72% delayed if absent (vs. 73%)
- ✓ Corpus Callosum
 - 96% delayed if hypoplastic (vs. 58%)
- ✓ Other major malformations
 - 100% delayed if present (vs. 68%)

Corpus Callosum and Developmental Disorders

- Corpus callosum area measurements much smaller in subjects with delay
- Increased risk of cognitive impairment - 2.7 (1.4-5.8) for each cm^2 decrement in corpus callosum area

Laterality & Developmental Delay

- Unilateral cases (18%)
 - 38.5% have developmental delay
- Bilateral cases (82%)
 - 78.3% have developmental delay

Septum Pellucidum & Hypopituitarism

- 39% missing the septum pellucidum
2/3 have endocrine dysfunction
- 61% have the septum pellucidum
3/4 have endocrine dysfunction

Corpus Callosum & Hypopituitarism

- Hypoplastic corpus callosum
76% have endocrine dysfunction
- Normal corpus callosum
70% have endocrine dysfunction

Endocrine Dysfunction & Developmental Delay

Any endocrine dysfunction

✓ 73.6% delayed (vs. 60% without dysfunction)

Hypothyroidism

✓ 93% delayed (vs. 51% with normal levels)

Newborn Thyroid Function

- Thyroid hormone essential for brain development in infants
- Newborn screening (NBS) for primary hypothyroidism (1/3000) mandatory in U.S.
- High ($>25\mu\text{IU}$) TSH reported by Calif. NBS
 - 94% sensitive for primary hypothyroidism
- Low TSH (associated with central hypothyroidism) not reported

Hypothyroidism in ONH

- Central hypothyroidism detected in ONH at mean age of 15 mos.
- Hypothyroidism is major risk factor for cognitive impairment in ONH
- Hypothyroidism can evolve
- Vision outcomes better in subjects without hypothyroidism

Management of ONH

- MRI of brain
- Fasting AM cortisol & glucose
- TSH, free T4, IGF-1, IGF-BP3
- Monitor growth q 6mo.
- GH stim test if slow growth
- Free T4, AM cortisol q 6mo. until age 2 yr; q 12mo. until age 5 yr.

Conclusions

- ONH is the hallmark of a congenital syndrome manifested by:
 - Poor vision in one or both eyes
 - Hypothalamic dysfunction
 - Developmental delay
 - Various neuroradiographic abnormalities
- “Septo-optic dysplasia” is a misleading and historically inaccurate term