Mikrosefali

Makrosefali

Tanı ve Yönetim

Prof. Dr. Cem Batukan

Acıbadem Üniversitesi Tıp Fakültesi

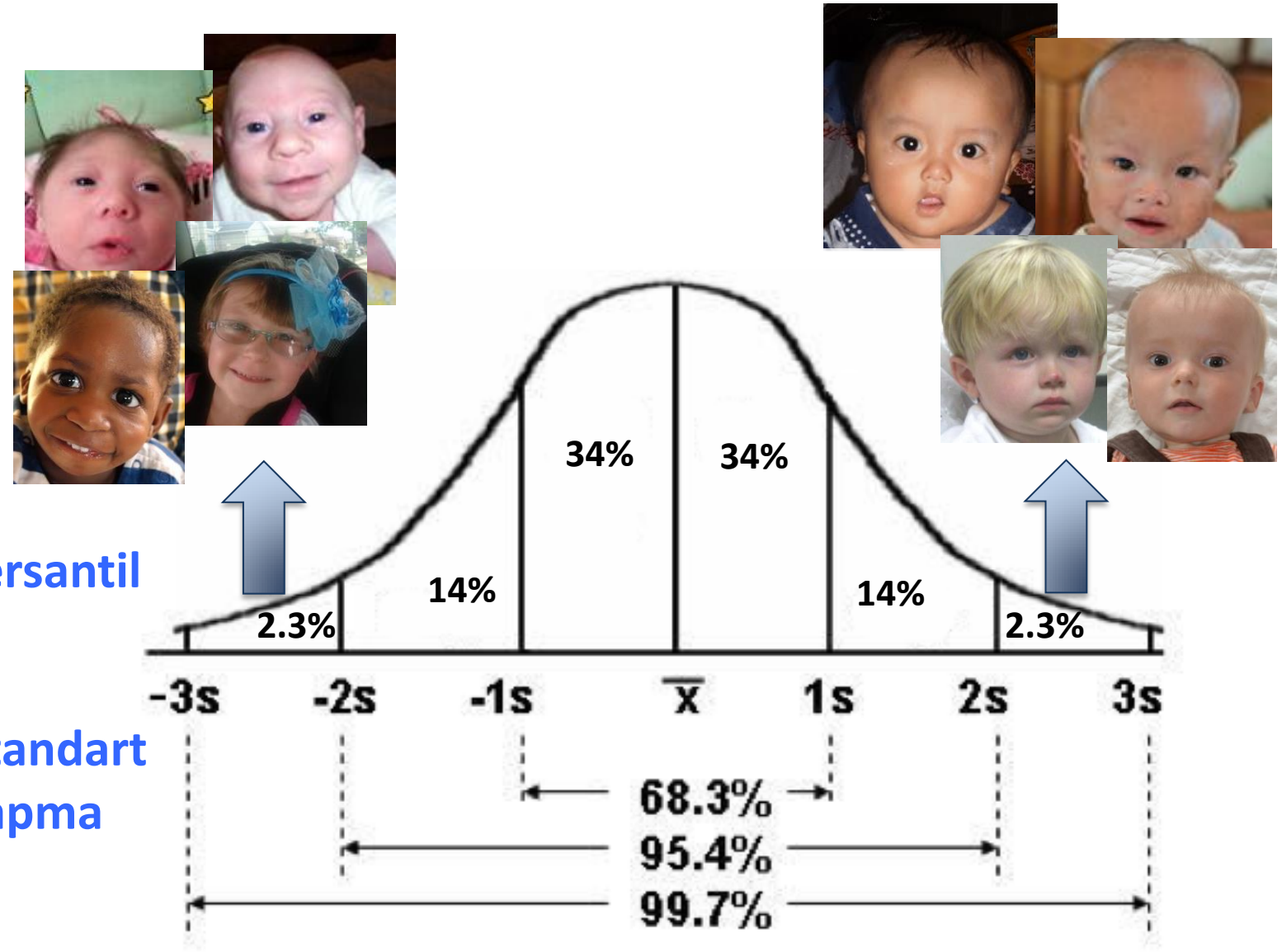
Kadın Hastalıkları ve Doğum ABD

cbatukan@gmail.com

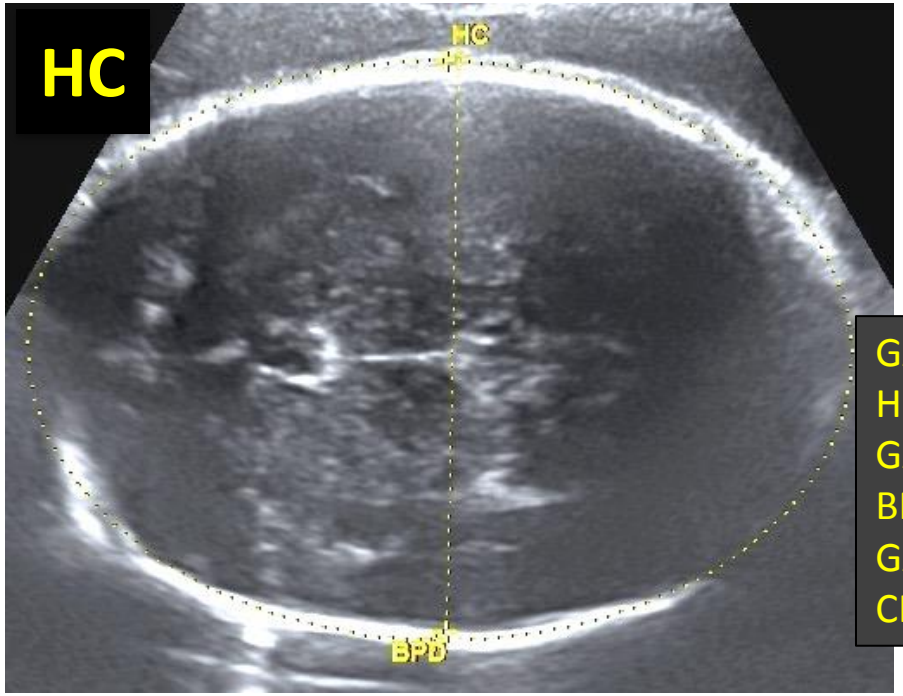
Terimler ve Tanımlar

- Mikrosefali ve makrosefali deskriptif terimlerdir; ultrason bulgusudur
  - Mikrosefali: küçük kafa
  - Makrosefali: büyük kafa
- Nöroradyolojij veya nöropatolojik tanı:
  - Mikroensefali: küçük beyin
  - Makroensefali (megalensefali): büyük beyin
- Beyin büyüklüğü kafa büyüklüğünü belirler:
  - Mikrosefali = mikroensefali
    - Tek istisna kraniyosinostoz: kafa kemikleri beyinin büyümesini kısıtlar
  - Makrosefali = makroensefali
    - hidrosefali, kafa içi yer kaplayan lezyonlar veya genişlemiş subaraknoid boşluk

Baş büyüklüğü



Mikrosefali - Tanım



GA: 38w4d
HC: 281mm
GA: 34w0d (<2.3%)
BPD: 83mm
GA: 33w3d (<2.3%)
CI (BPD/OFD): 68%

~~HC/FL~~
~~HC/AC~~

- Pediatrik popülasyon HC < -2SD (%2.3 persantil):
  - Insidans %2.3
  - birçok normal olgu
- Prenatal popülasyon HC < -3SD (%0.2 persantil):
  - insidans %0.16
  - Doğumda bildirilen semptomatik mikrosefali sıklığına (14/10.000) daha yakın

HC – Referans çizelgeleri

36 hafta

Yazar	50. persantil	-2SD	2,3. persantil
Chervenak ✔	325	30	295
Hadlock*	328	19	309
Chitty	325	25	300
Verburg	324	22	302
Leung	318	20	298
Johnsen	320	25	295
Paladini	320	26	294
Kurmanavicius	320	26	294

*Hadlock et al., Fetal head circumference: relation to menstrual age. AJR Am J Roentgenol. 1982

Ioannou et al., Systematic review of methodology used in ultrasound studies aimed at creating charts of fetal size. BJOG, 2012

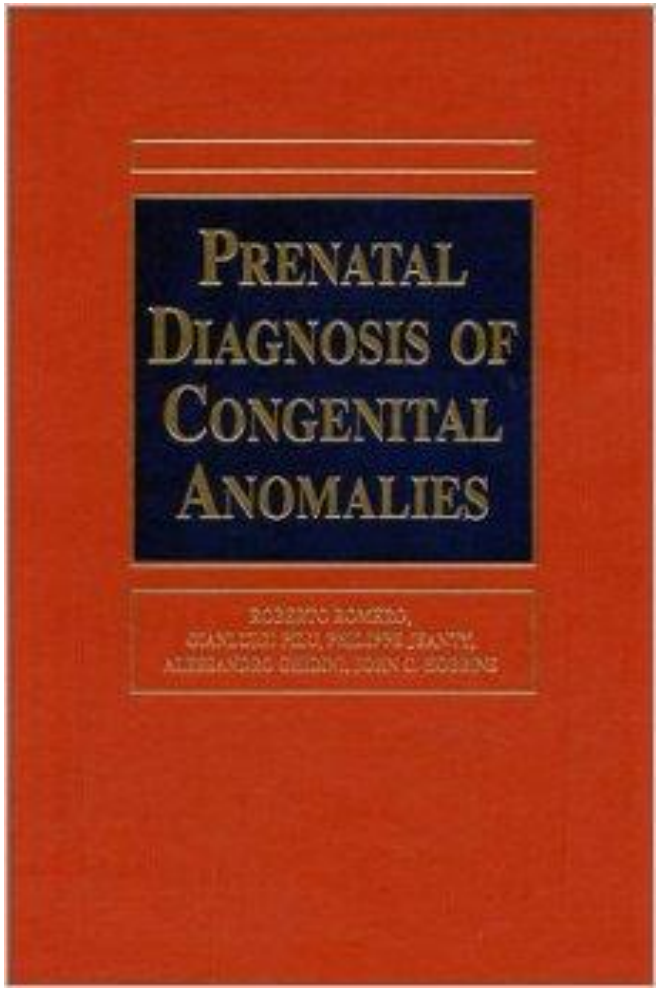


TABLE 1–15. HEAD PERIMETER

Age (weeks)	Head Perimeter (mm)					
	50th	*−1SD*	*−2SD*	*−3SD*	*−4SD*	*−5SD*
11	63	48	33	19	4	—
12	75	61	46	31	17	2
13	88	73	59	44	29	15
14	101	86	71	57	42	27
15	113	99	84	69	55	40
16	126	111	96	82	67	52
17	138	124	109	94	80	65
18	151	136	121	107	92	77
19	163	148	133	119	104	89
20	175	160	145	131	116	101
21	187	172	157	143	128	113
22	198	184	169	154	140	125
23	210	195	180	166	151	136
24	221	206	191	177	162	147
25	232	217	202	188	173	158
26	242	227	213	198	183	169
27	252	238	223	208	194	179
28	262	247	233	218	203	189
29	271	257	242	227	213	198
30	281	266	251	236	222	207
31	289	274	260	245	230	216
32	297	283	268	253	239	224
33	305	290	276	261	246	232
34	312	297	283	268	253	239
35	319	304	289	275	260	245
36	325	310	295	281	266	251
37	330	316	301	286	272	257
38	335	320	306	291	276	262
39	339	325	310	295	281	266
40	343	328	314	299	284	270

SD = standard deviation.

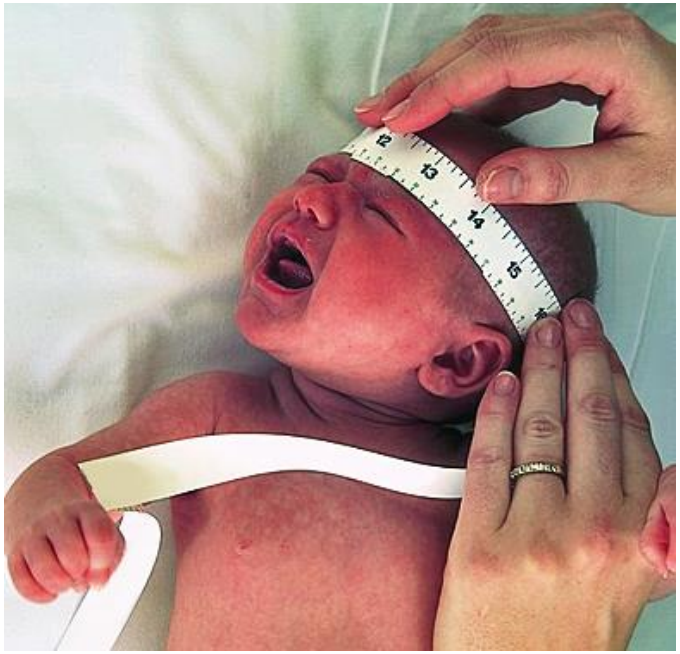
Chervenak et al. Am J Obstet gynecol 1987

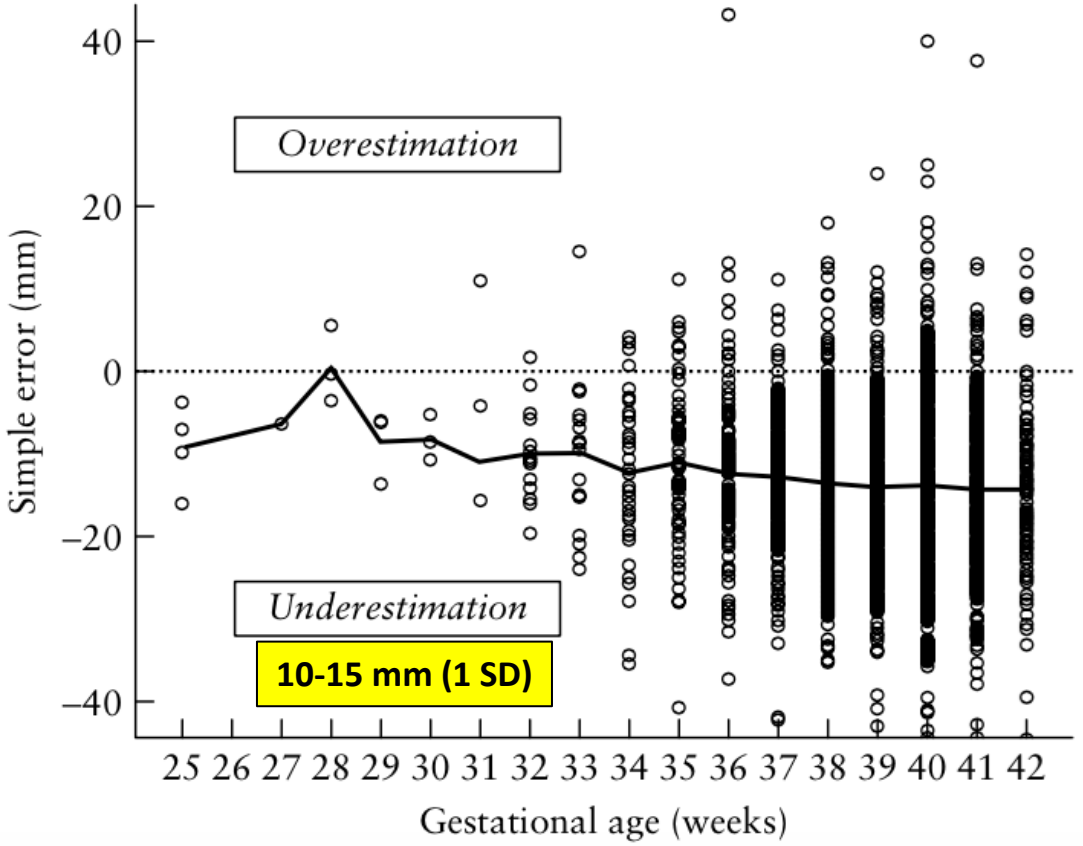
Sonographic estimation of fetal head circumference: how accurate are we?

N. MELAMED, Y. YOGEV, D. DANON, R. MASHIACH, I. MEIZNER and A. BEN-HAROUSH

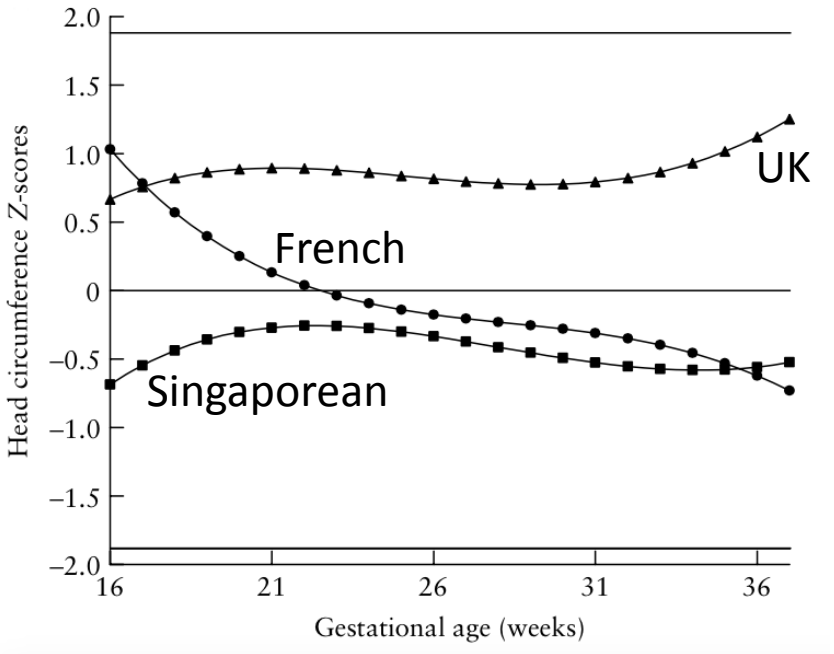
Department of Obstetrics and Gynecology, Helen Schneider Hospital for Women, Rabin Medical Center, Petach Tikva and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Ultrasound Obstet Gynecol 2011; **37**: 65–71
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.7760





Etnik ve Cinsiyet



Female HC				Male HC			
GA (weeks)	*Mean (mm)*	*SD (mm)*	*Frequency (n)*	*GA (weeks)*	*Mean (mm)*	*SD (mm)*	*Frequency (n)*
15	114.60	3.72	10	15	116.73	4.15	10
16	128.32	6.37			55	8.62	17
17	139.56	5.40			97	6.72	17
18	153.35	7.25			62	6.84	81
19	167.96	7.57			28	8.93	65
20	176.90					7.20	486
21	187.25					8.52	260
22	199.24					8.68	185
23	209.12					9.51	51
24	221.99					9.73	87
25	231.56					8.64	42
26	243.54					7.99	49
27	255.49					12.68	41
28	263.42					11.12	89
29	275.54					12.42	65
30	282.97					10.52	61
31	291.20					12.15	81
32	300.13					11.67	134
33	305.58					11.93	109
34	312.17					12.34	190
35	315.26	13.51			0.62	13.70	119
36	321.58	13.10			6.94	12.42	146
37	324.55	13.81			1.08	12.99	102
38	327.23	12.62	81	38	334.72	14.77	69
39	330.94	11.33	42	39	335.54	13.28	33
Total			2466	Total			2589

kız

erkek

35 315.26 320.62

36 321.58 326.94

37 324.55 331.08

38 327.23 334.72

39 330.94 335.54

5mm ≈ 1 hafta

Leung et al., Fetal biometry in ethnic Chinese: biparietal diameter, head circumference, abdominal circumference and femur length.UOG, 2008

Schwaerzler et al., Sex-specific antenatal reference growth charts for uncomplicated singleton pregnancies at 15-40 weeks of gestation., UOG, 2004

Mikrosefali sınıflaması

Etyoloji

A. Genetik
B. Çevresel faktörlere bağlı edinsel

Ortaya çıkış zamanı (en sık kullanılan sınıflama)

A. Konjenital (primer): doğumda mevcut olan
B. Postnatal (sekonder): doğum sonrası ortaya çıkan

Eşlik eden ek anomali

A. İzole
B. Sendromik (veya kompleks): + ek yapısal anomali

Mikrosefali-Patogenez

Çevresel nedenler

- ***Hipoksik-iskemik ensefalopati (serebral palsi)***
- ***Yıkıcı etkiler (ör: monozigotik ikiz eşin intrauterin ölümüne bağlı vasküler problemler)***
- ***İntrauterin enfeksiyonlar***
  - Rubella
  - CMV
  - Toksoplazma
  - Varicella zoster
- ***Teratojenler***
  - Alkol
  - Hydantoin
  - Radyasyon
  - Solvent maruziyeti (ör: toluen, akaryakıt)
  - CO zehirlenmesi
- ***Kontrolsüz maternal Fenilketonüri***
- ***Kötü glisemik kontrollü diyabet***

Genetik nedenler

- ***İzole***
  - Otozomal resesif mikrosefali (MCPH)
  - Otozomal dominant mikrosefali (del 1q21.1)
  - X'e bağlı mikrosefali (Xq12-q21.31)
  - Kromozomal (nadir; dengeli translokasyon gibi görünen kromozomal değişiklikler ve halka krom.)
- ***Sendromik mikrosefali***
  - Kromozom anomalileri
    - Trizomi 21
    - Trizomi 13
    - Trizomi 18
  - Kontinü gen delesyon sendromları
    - 5p delesyon (cri-du-chat) sendromu
    - 4p delesyon (Wolf-Hirschhorn) sendromu
    - 18p and 18q delesyon sendromu
    - 7q11.23 delesyon (Williams) sendromu
    - 17p13.3 delesyon (Miller-Dieker) sendromu
  - Multiple anomalilerin eşlik ettiği diğer sendromlar
    - Dubowitz sendromu
    - Feingold sendromu
    - Cornelia de Lange sendromu
    - Smith-Lemli-Opitz sendromu
    - Holoprosencephaly (izole ve sendromik)
    - Seckel sendromu
  - OMİM de listelenmiş >470 sendrom

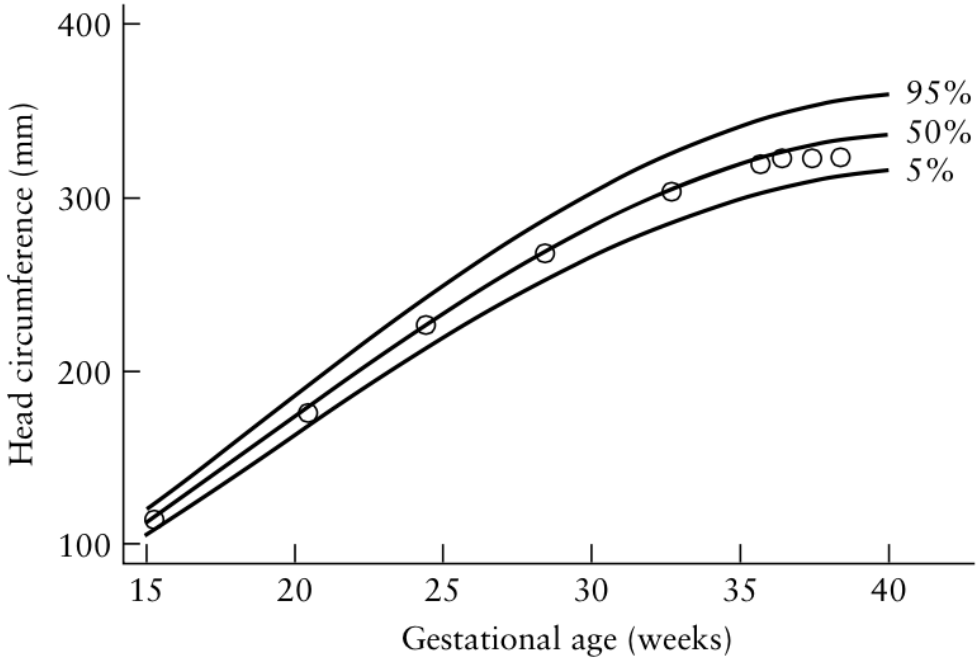
Congenital microcephaly detected by prenatal ultrasound: genetic aspects and clinical significance

N.S. DEN HOLLANDER, M.W. WESSELS*, F.J. LOS*, N.T.C. URSEM, M.F. NIERMEIJER* and J.W. WLADIMIROFF

- Antenatal mikrosefali tanısı (n=30)
  - İzole (%16.7)
  - Holoprosensefali (%16.7)
  - Kromozom anomalisi (%23.3)
  - Sendrom (%20)
  - Multiple anomali (%23.3)

Den Hollander et al., UOG, 2000

İzole mikrosefali – geç tanı



- Çoğu olgunun tanısı prenatal dönemde konamıyor
  Mikrosefali olgularının yaklaşık 1/8 inde mikrosefali doğumda mevcut; 7/8'inde mikrosefali sonraki yıllarda ortaya çıkıyor
- Gebelikte HC -1 ile -2 SD olan fetuslarda doğum sonrası mikrosefalik riski daha yüksek

Establishment of Fetal Biometric Charts Using Quantile Regression Analysis

Etty Daniel-Spiegel, MD, Ehud Weiner, MD, Ilan Yarom, MD, Etti Doveh, PhD, Perry Friedman, MD, Ayala Cohen, PhD, Eliezer Shalev, MD

17,708 sonographic examinations of pregnant between 12 and 42 weeks of pregnancy

In 261 pregnancies (1.5%) a diagnosis of isolated microcephaly was suspected on the basis of measurements of the head circumference alone

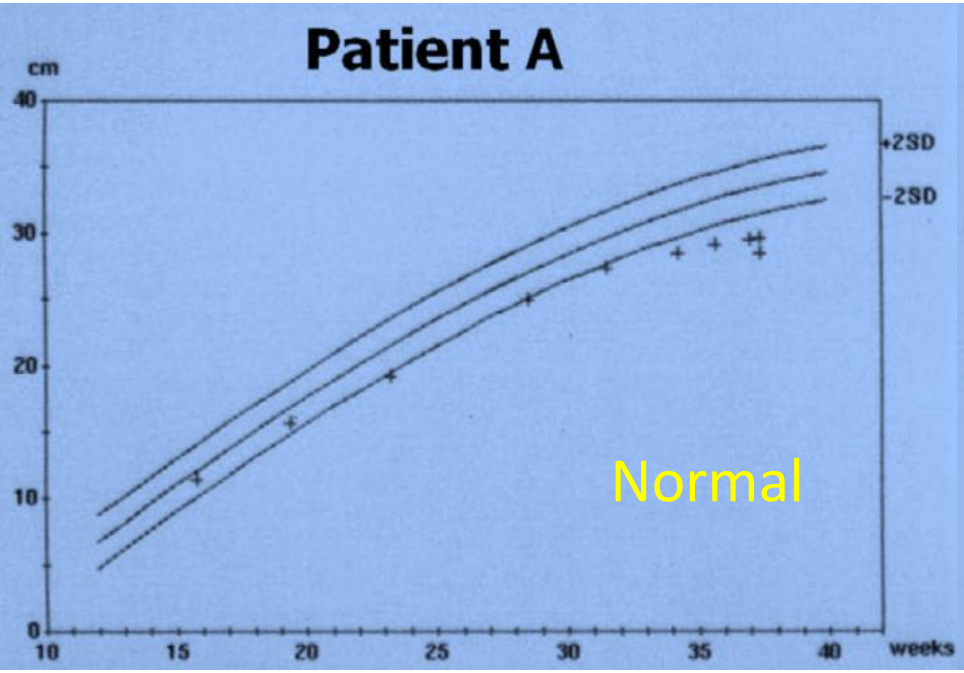
A total of 13 children (0.07%) were ultimately as having true pathologic microcephaly (defined as a small head circumference accompanied by postnatal neurologic impairment in the absence of other physical anomalies).

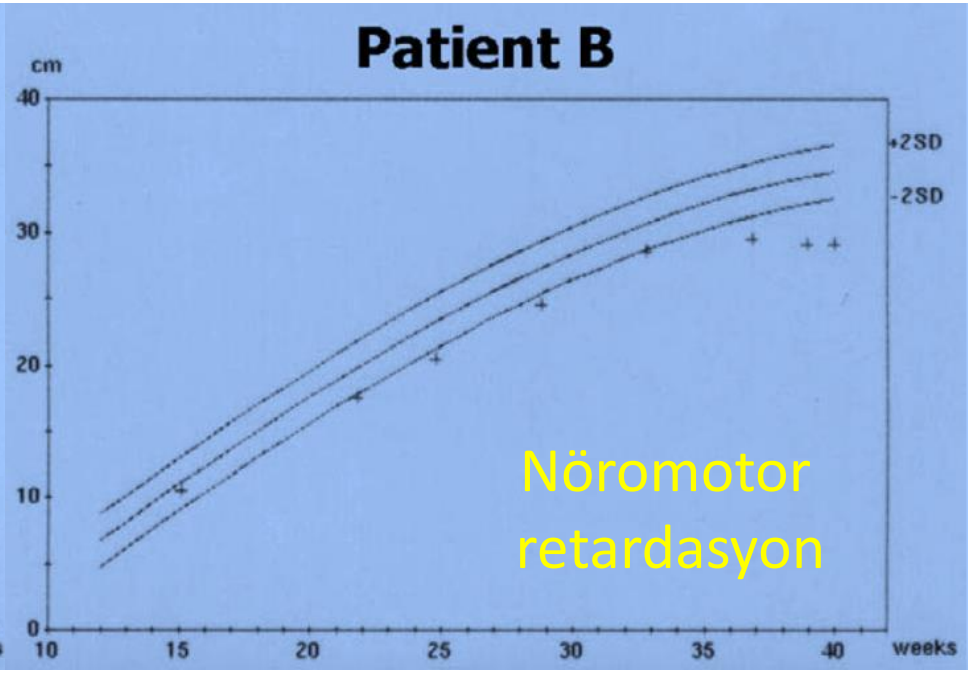
A total of 248 false positives (normal head circumference after delivery and normal development)

19 TOP for one true symptomatic microcephaly

J Ultrasound Med 2013; 32:23–33

Hangisi normal?





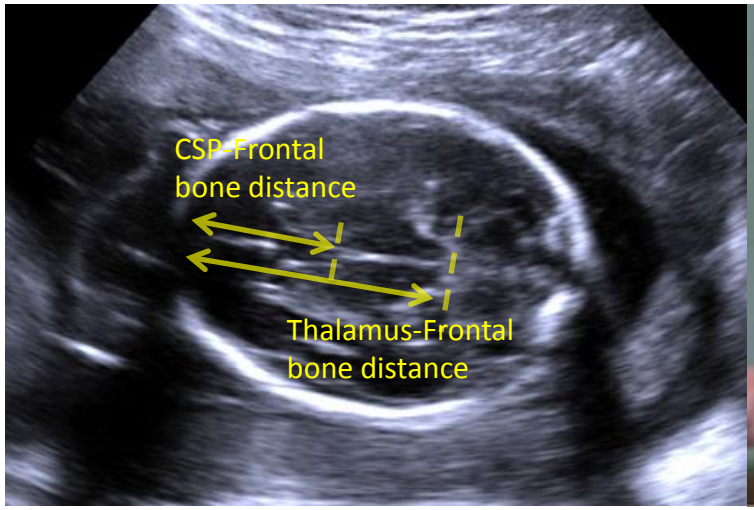
- Annenin baş çevresi küçük (51 cm) ve zekası normal

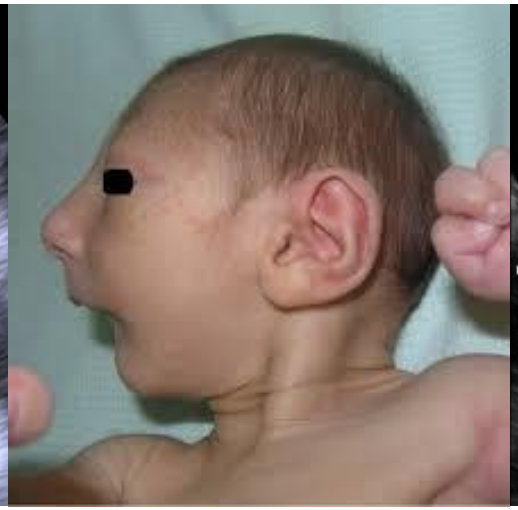
- Hastanın ağır mikrosefalili ve IQ'su düşük bir kardeşi var
- Anne baba akraba

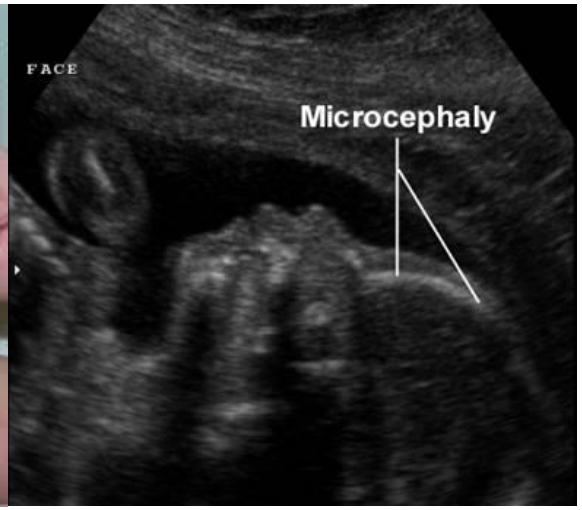
Malinger et al., Reproductive Biology and Endocrinology 2003

Küçük beyin yapısı ile doğrudan ilişkili ultrason bulguları

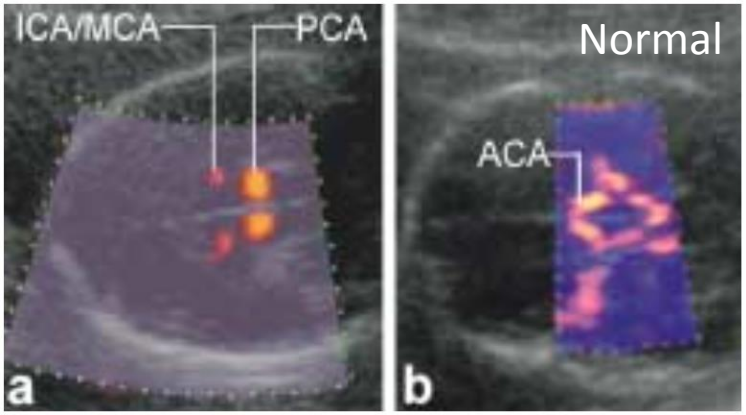
Küçük frontal loblar / “sloping forehead”



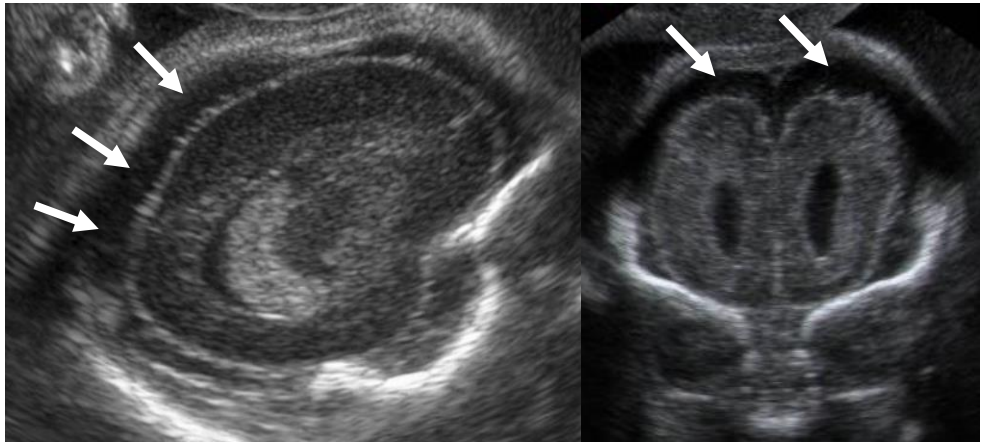




Azalmış frontal lob kan akımı

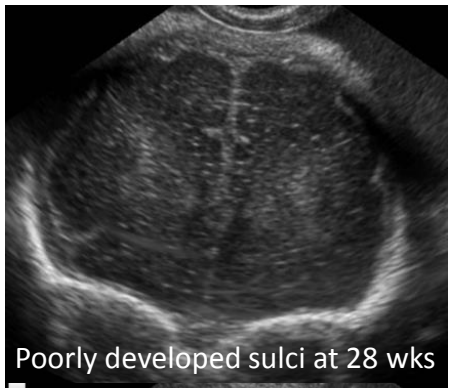


Genişlemiş subaraknoid alan

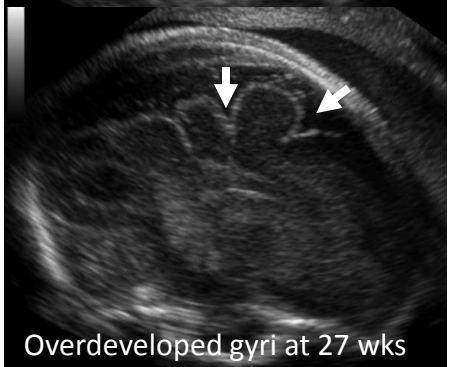


Kortikal gelişim bozukluğu bulguları

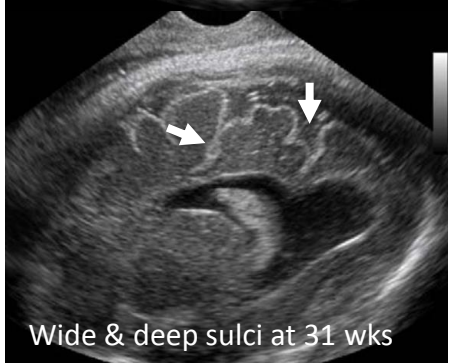
Anormal sulkasyon & gyrasyon



Poorly developed sulci at 28 wks

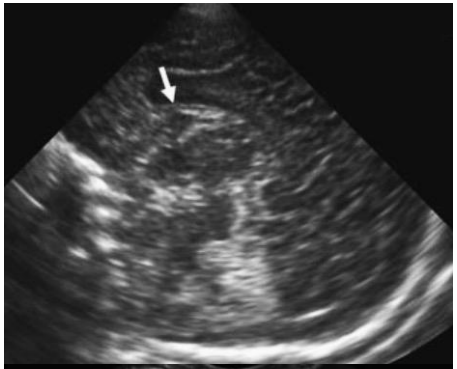


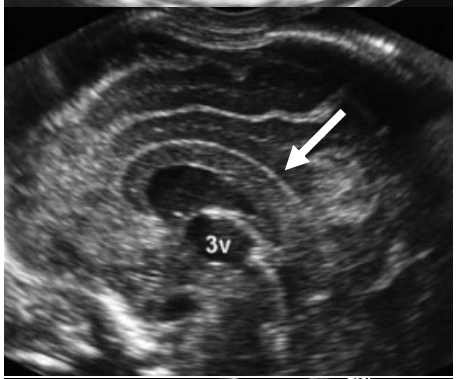
Overdeveloped gyri at 27 wks

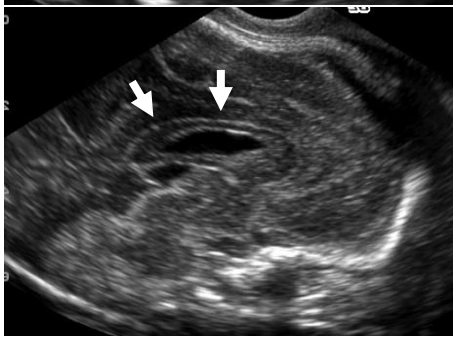


Wide & deep sulci at 31 wks

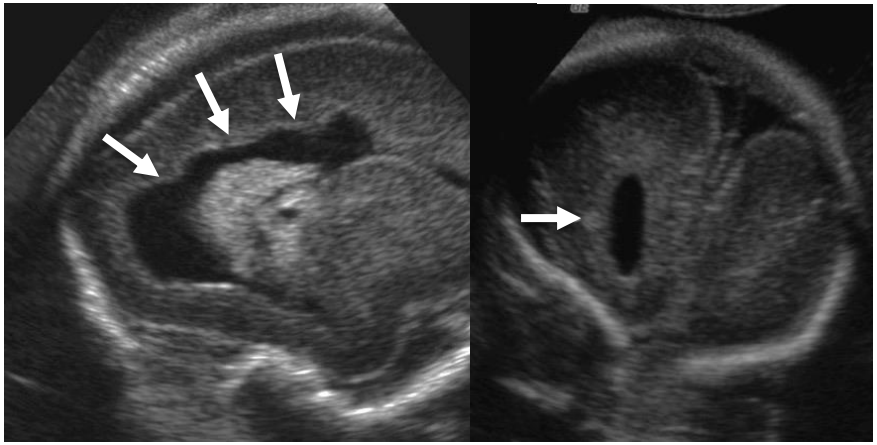
Callosal anomaliler



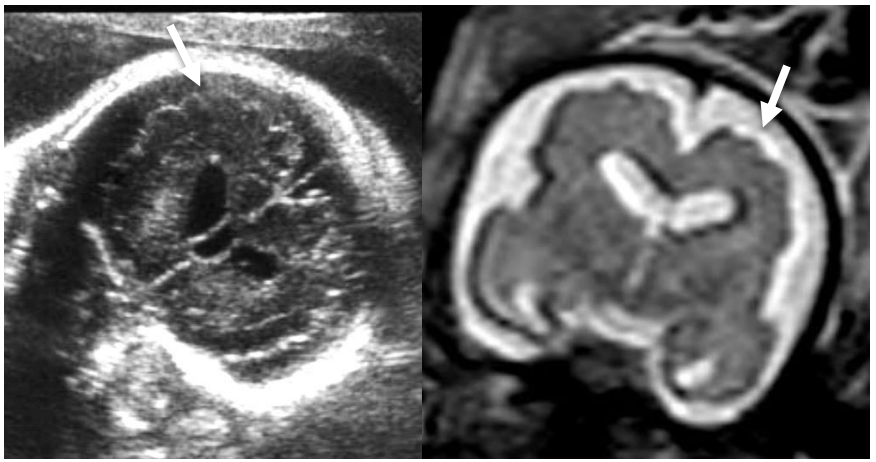




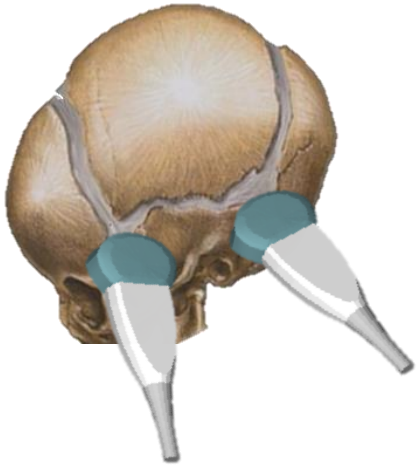
Periventrikülar nodülar heterotopi



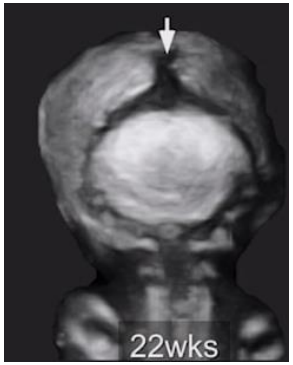
Polimikrogyri



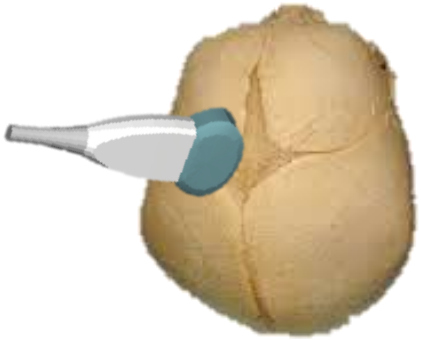
Detaylı MSS incelemesi: Sutura ve fontaneller



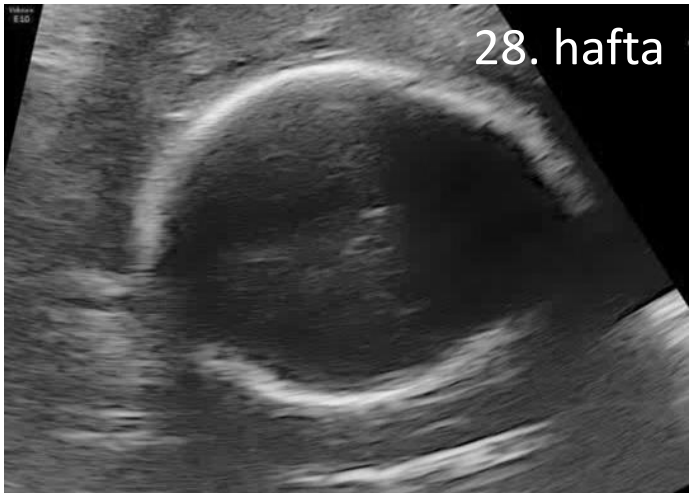
Mastoid & Sfenoid Fontanel

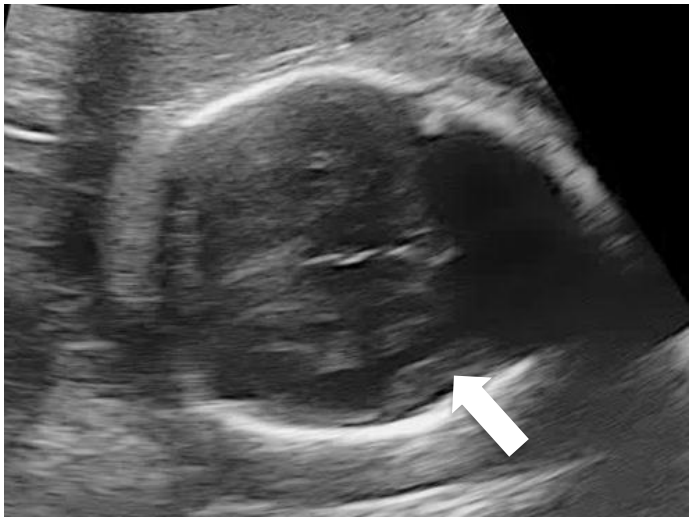


Occipital Fontanel



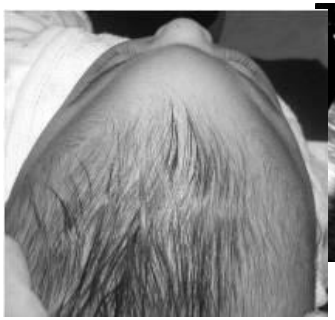
Anterior Fontanel

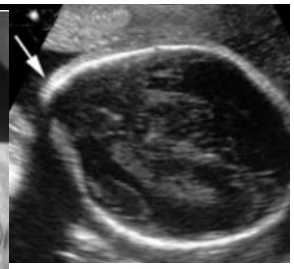


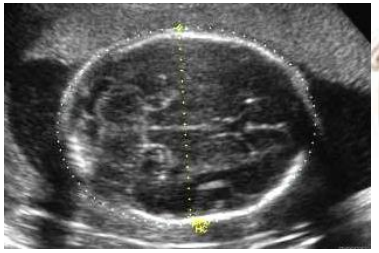


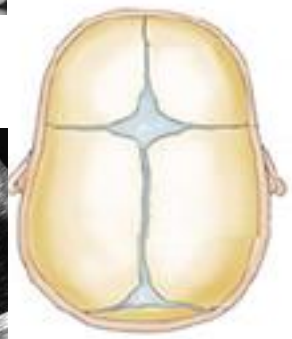
Dx: Kraniosinostoz

Trigonosefali



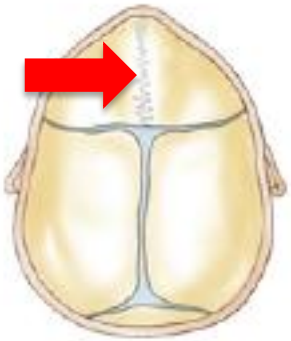




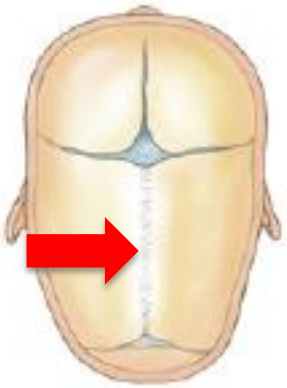


Normal

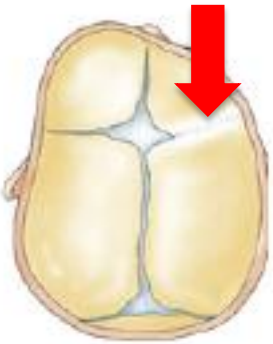
Plagiosefali



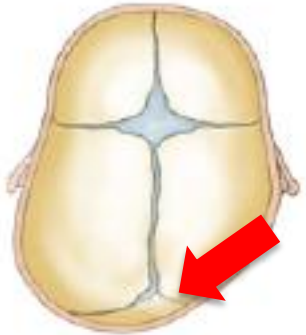
Metopic



Sagittal

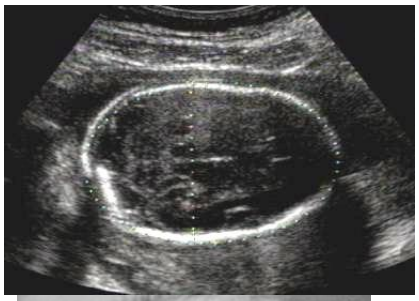


Unicoronal

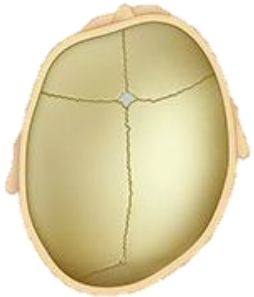


Lambdoid

Skafosefali



Lambdoid sinostoz

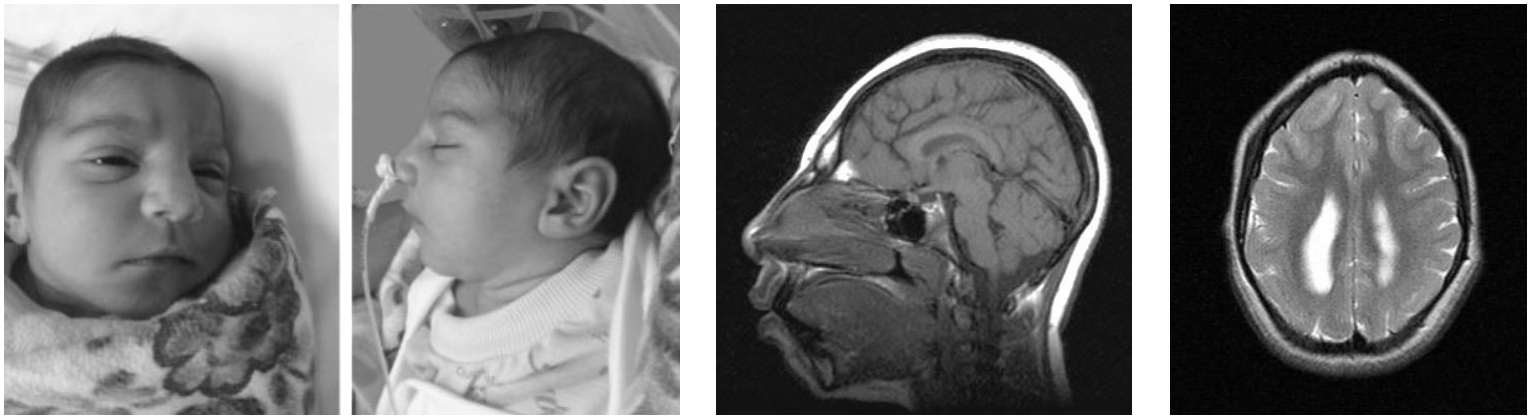


Sagital > Koronal > Metopik > Lambdoid

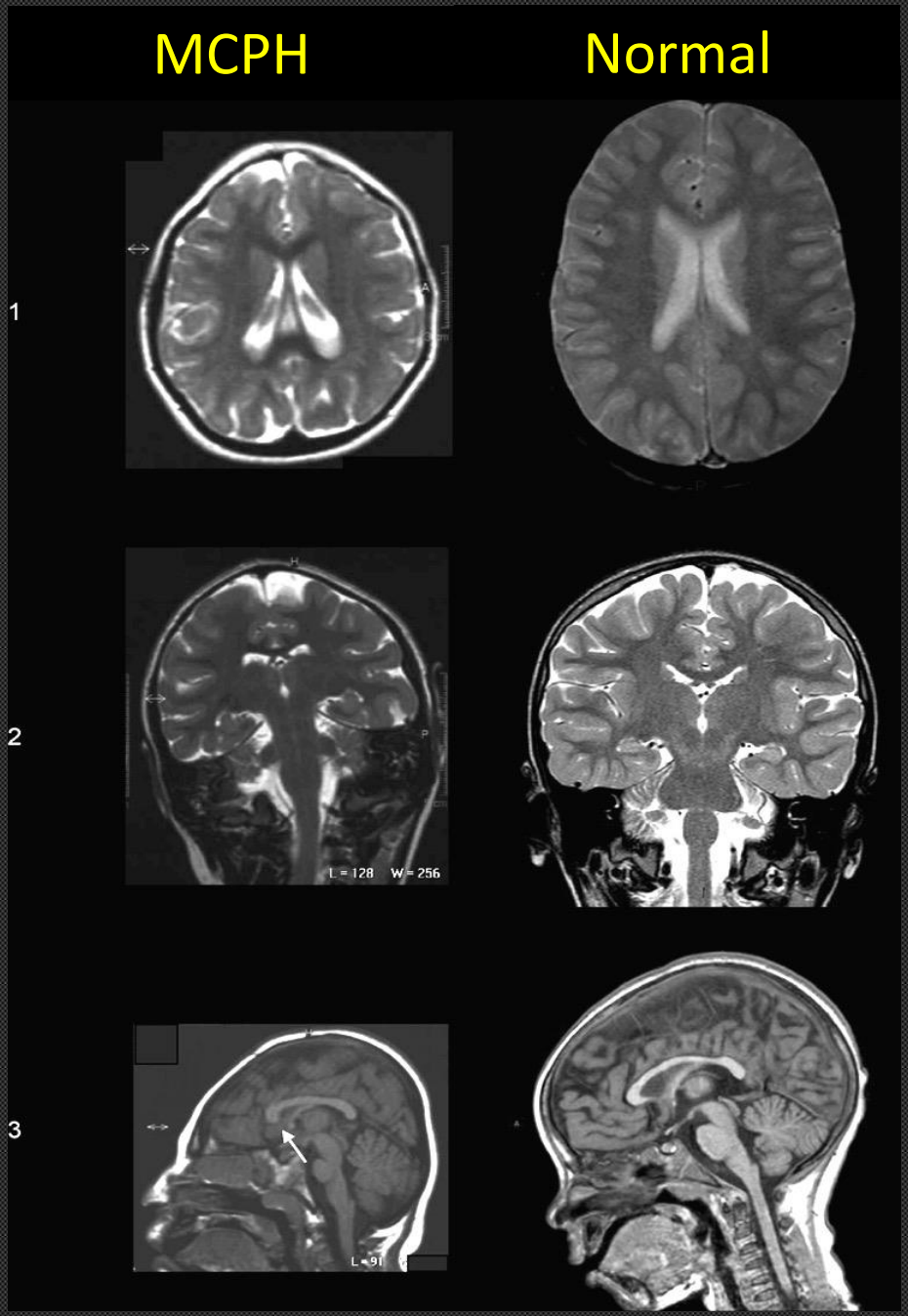
Mikrosefali tipleri

- **Primer mikrosefali:**
  - Doğuştan var olan, konjenital
- **Sendromik mikrosefali:**
  - Sendromlarla ilişkili olan
- **Edinsel mikrosefali:**
  - Normal gelişen beyinin sonradan hasara uğraması sonucu oluşan mikrosefali

MCPH=***M***icro***C***ephaly ***P***rimary ***H***ereditary
"microcephaly vera"



- Otozomal resesif; bilinen en az 15 mutasyon var; **sıklık: 1/30.000-250.000**
  İzole; diğer organ sistemlerinde anomali veya dismorfik bulgular eşlik etmez; IUGG olağan
- Genelde doğumda mikrosefali mevcut; çoğu zaman başın büyümesi terme yakın dönemde (32. hafta civarında) yavaşlar
- Nadiren doğumda HC normalin alt sınırındadır (ASPM gen mutasyonu)
- Doğum sonrası ileri derecede yavaş beyin gelişimi; HC -4SD/-12SD
- Görüntülemede beyin çoğunlukla normal görünür veya **"**simplified gyral pattern" veya hafif ventrikülomegali eşlik edebilir
- Zeka: hafif-orta derecede mental retardasyon (non-progresif); başka nörolojik bulgu yok


MCPH
Normal
1
2
3
L = 128 W = 256
L = 91

MCPH: Genetik heterojenite

Phenotypic Series OMIM

Download As

Microcephaly, primary autosomal recessive - PS251200 - 15 Entries

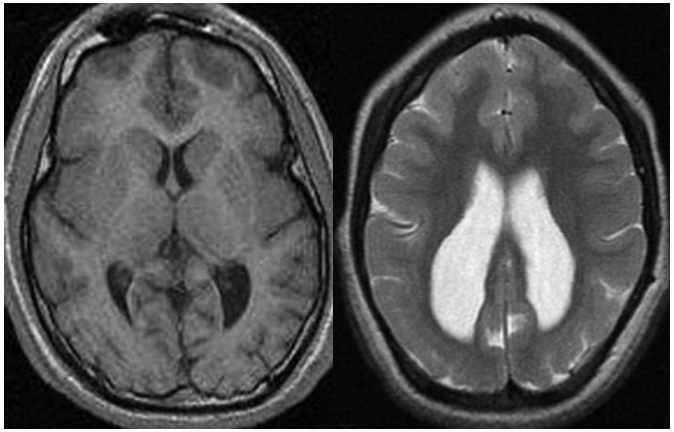
Location ▲	Phenotype	Phenotype mapping key	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
1p34.2	Microcephaly 15, primary, autosomal recessive	3	616486	MFSD2A, MCPH15	614397
1p33	Microcephaly 7, primary, autosomal recessive	3	612703	STIL, SIL, MCPH7	181590
1p21.2	?Microcephaly 14, primary, autosomal recessive	3	616402	SASS6, SAS6, MCPH14	609321
1q31.3	Microcephaly 5, primary, autosomal recessive	3	608716	ASPM, MCPH5	605481
4q12	?Microcephaly 8, primary, autosomal recessive	3	614673	CEP135, KIAA0635, MCPH8	611423
4q24	?Microcephaly 13, primary, autosomal recessive	3	616051	CENPE, MCPH13	117143
7q21.2	?Microcephaly 12, primary, autosomal recessive	3	616080	CDK6, PLSTIRE, MCPH12	603368
8p23.1	Microcephaly 1, primary, autosomal recessive	3	251200	MCPH1	607117
9q33.2	Microcephaly 3, primary, autosomal recessive	3	604804	CDK5RAP2, KIAA1633, MCPH3	608201
12p13.31	?Microcephaly 11, primary, autosomal recessive	3	615414	PHC1, EDR1, HPH1, RAE28, MCPH11	602978
13q12.12	Microcephaly 6, primary, autosomal recessive	3	608393	CENPJ, CPAP, MCPH6, SCKL4	609279
15q15.1	Microcephaly 4, primary, autosomal recessive	3	604321	CASC5, AF15Q14, KIAA1570, D40, MCPH4	609173
15q21.1	Microcephaly 9, primary, autosomal recessive	3	614852	CEP152, KIAA0912, MCPH9, SCKL5	613529
19q13.12	Microcephaly 2, primary, autosomal recessive, with or without cortical malformations	3	604317	WDR62, C19orf14, MCPH2	613583
20q13.12	?Microcephaly 10, primary, autosomal recessive	3	615095	ZNF335, NIF1, NIF2, MCPH10	610827

Batı Avrupa ve kuzey Amerika populasyonun %50-75'inde MCPH'nin genetik lokusu bilinmiyor

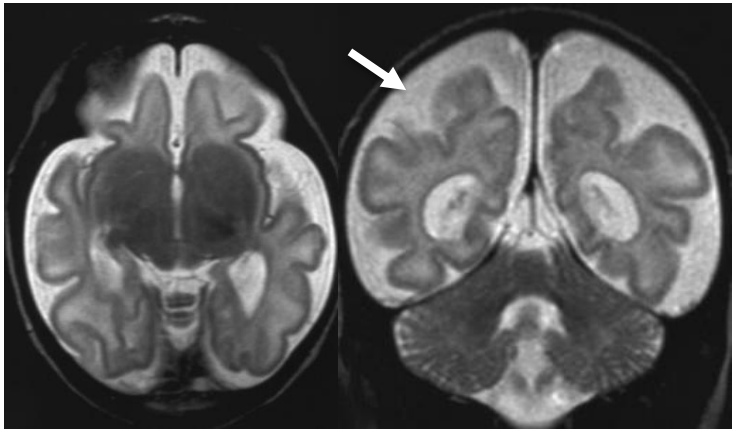
Primer Mikrosefali Alttipleri (MRI)

Basel-Vanagaite & Dobyns [2010]

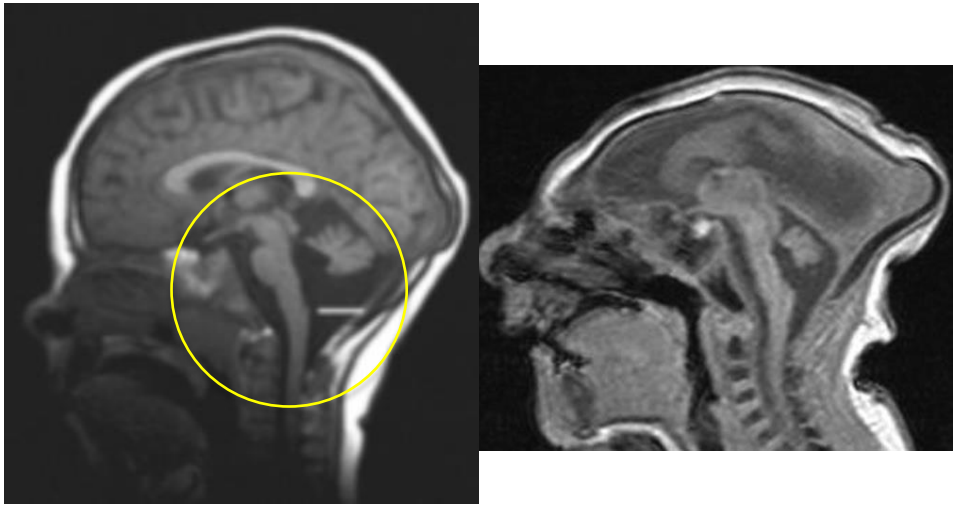
Simplified gyral pattern (SGP) only



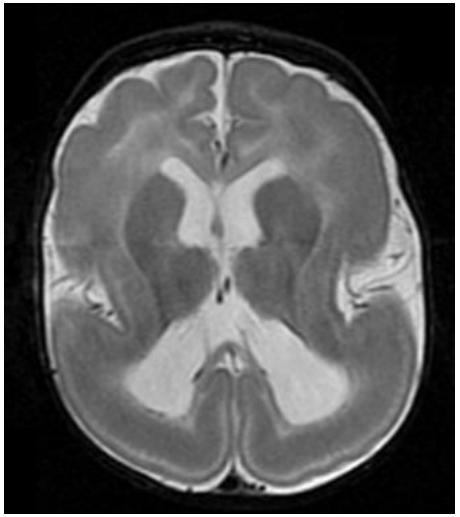
SGP + enlarged extraaxial space (EAS)



SGP/EAS + Pontocerebellar hypoplasia



Microlissencephaly (Lis plus Mic)



Sendromik mikrosefali

- Mikrosefaliye diğer organ sistemlerinde anomali, dismorfism ve/veya IUGG nin eşlik ettiği genetik hastalıklar
- Bulgular gebelikte, doğumda veya postnatal dönemde görülür
- Beyin görüntülemesi normal olabilir veya nonspesifik bulgular taşıyabilir
- Zeka: orta – ağır derecede mental retardasyon
- Eşlik eden diğer bulgular için detaylı ultrason incelemesi gerekir

Sendromik mikrosefali

- McKusick's Catalog of Mendelian Inheritance in Man (OMIM)
- London Dysmorphology Database
- Possum (www.possum. net.au)
- Smith's Recognizable Patterns of Human Malformation
- Gene Reviews (www.genetests.org)

Miller–Dieker syndrome → Microcephaly, ventriculomegaly + lissencephaly, cardiac anomalies, facial anomalies and polydactyly

Walker–Warburg syndrome → ventriculomegaly + eye anomalies (microphthalmia, cataract), CNS anomalies (lissencephaly, midline anomalies, cerebellar anomalies, microcephaly, and cephalocele)

Neu–Laxova syndrome → DWM + lissencephaly, **microcephaly**, proptosis, diffuse joint contractures, subcutaneous tissue edema, and **intrauterine growth retardation**

Smith–Lemli–Opitz syndrome → microcephaly + genitourinary defects (hypospadias and cryptorchidism), syndactyly

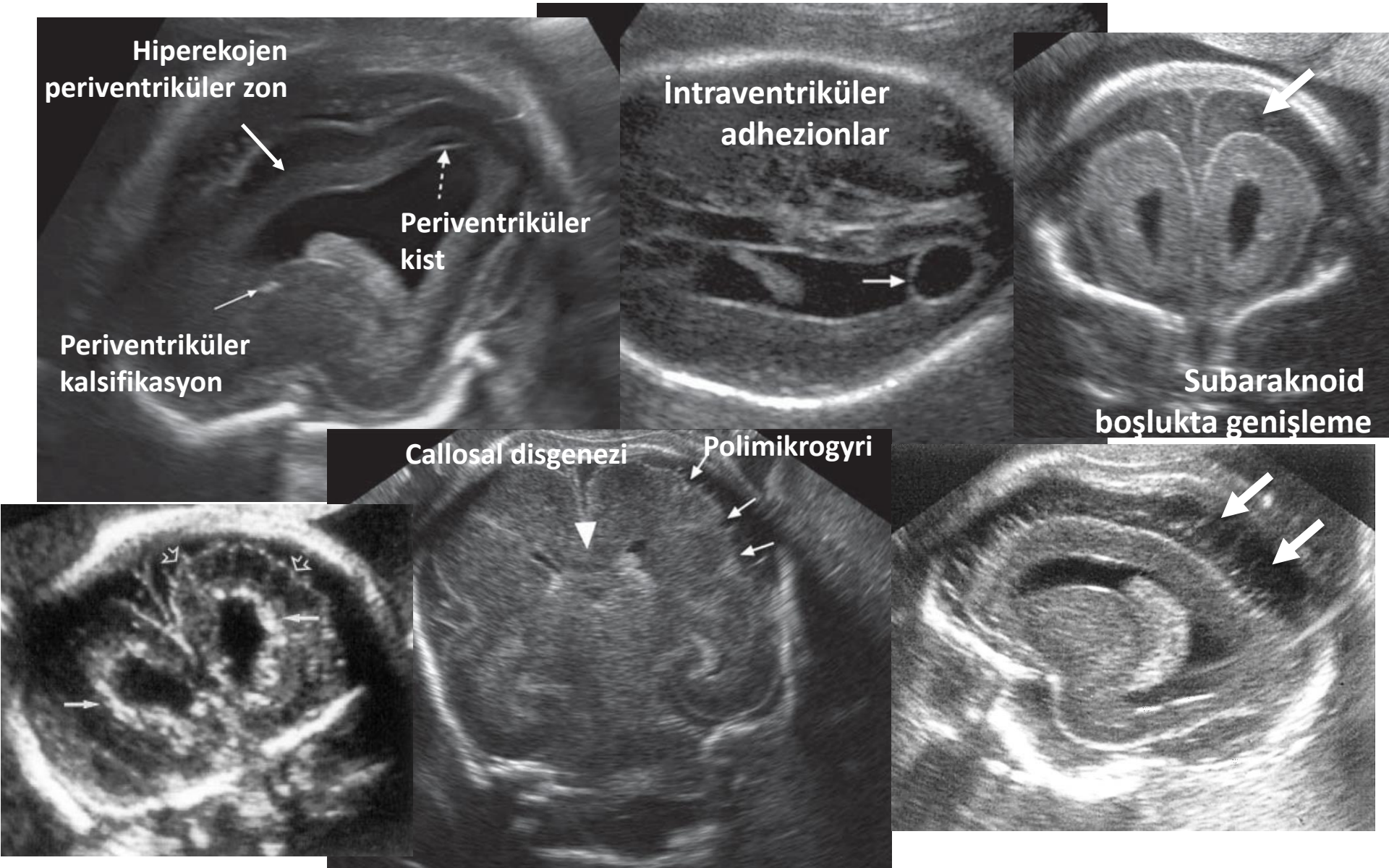
Seckel syndrome → **microcephaly + intrauterine growth retardation** and facial anomalies

Meckel–Gruber syndrome → polycystic kidney + cephalocele, microcephaly, polydactyly

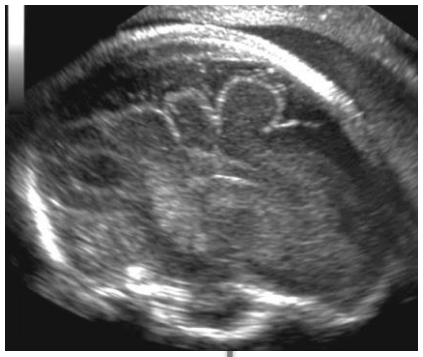
Edinsel mikrosefali

- Normal gelişim göstermiş olan beyinin sonradan yıkıma uğraması
- Süreç İntrauterin veya doğum sonrası başlayabilir
- Nedenler:
  - Enfeksiyonlar
  - İskemi
  - Teratojen ve toksinler
  - Metabolik bozukluklar
- Genelde başka anomali eşlik etmez

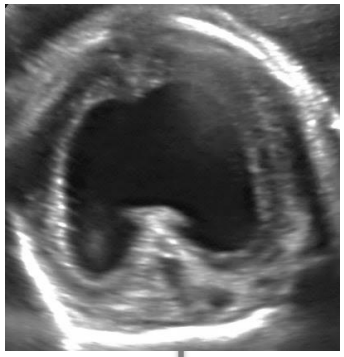
CMV enfeksiyonu



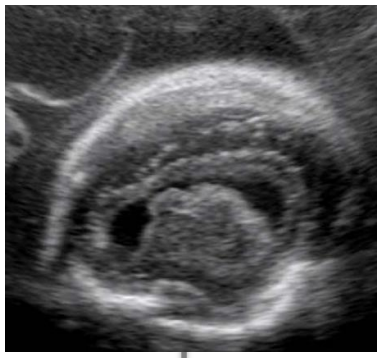
Kortikal gelişim bozukluğu



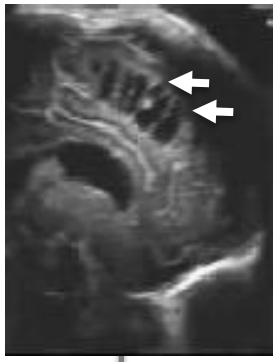
Holoprosensefali



Serebral atrofi



Subkortikal kist



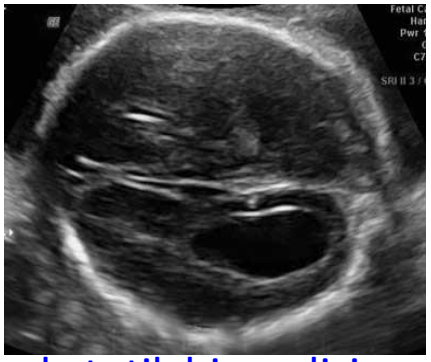
Aile öyküsü

Düşük serum estriol

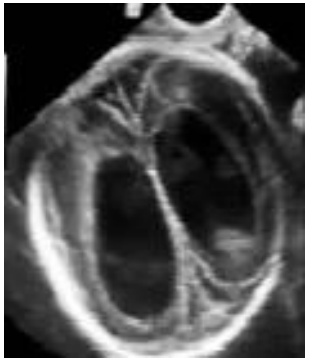
Metabolik Hastalıklar

MSS dışı anomaliler

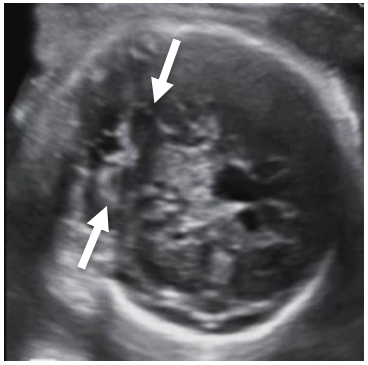
Callozal disgenezi



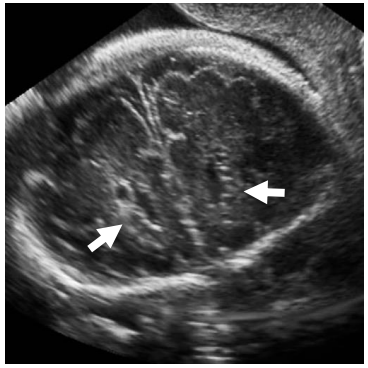
Ventrikülomegali



Serebellar hypoplazi



PV Pseudokist

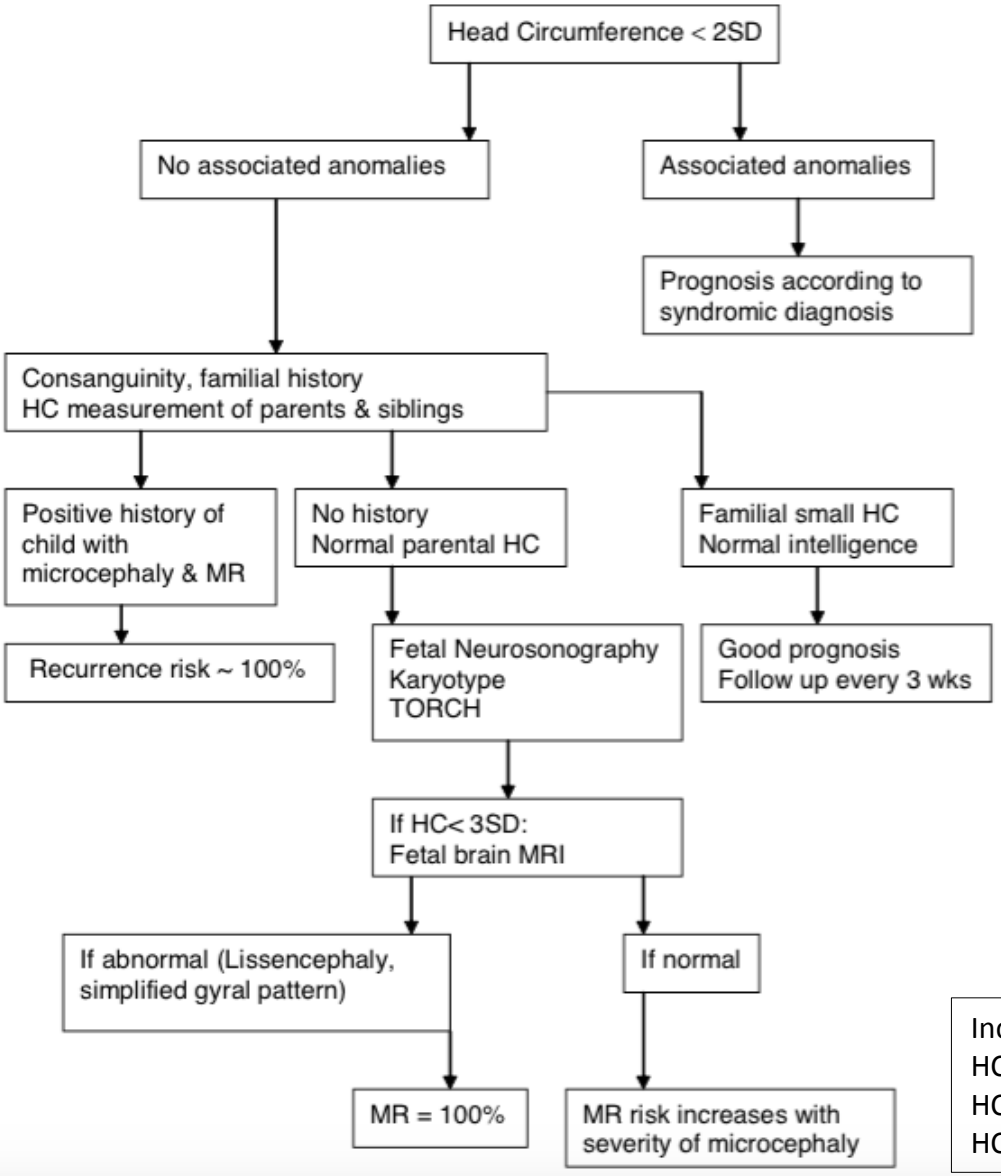


Nonketotik hiperglisinemi

Mikrosefali prenatal yönetim

- Detaylı US (kranial ve/veya ekstrakranial anomaliler)
- Fetal MR (beyinde ek malformasyon / gyral pattern)
- Genetik danışma
  - Akrabağlık
  - Anne/baba ve kardeşlerin baş çevresi
  - Sendromik mikrosefali
- Karyotip
  - Konvansiyonel
  - Mikrodelesyonlar için FISH (US'de sendrom düşündüren bulgu varlığında)
  - array CGH: + %4-5 kromozomal anomali
- Maternal TORCH serolojisi ve/veya amniyotik sıvı PCR

Flow chart in patients with suspected microcephaly

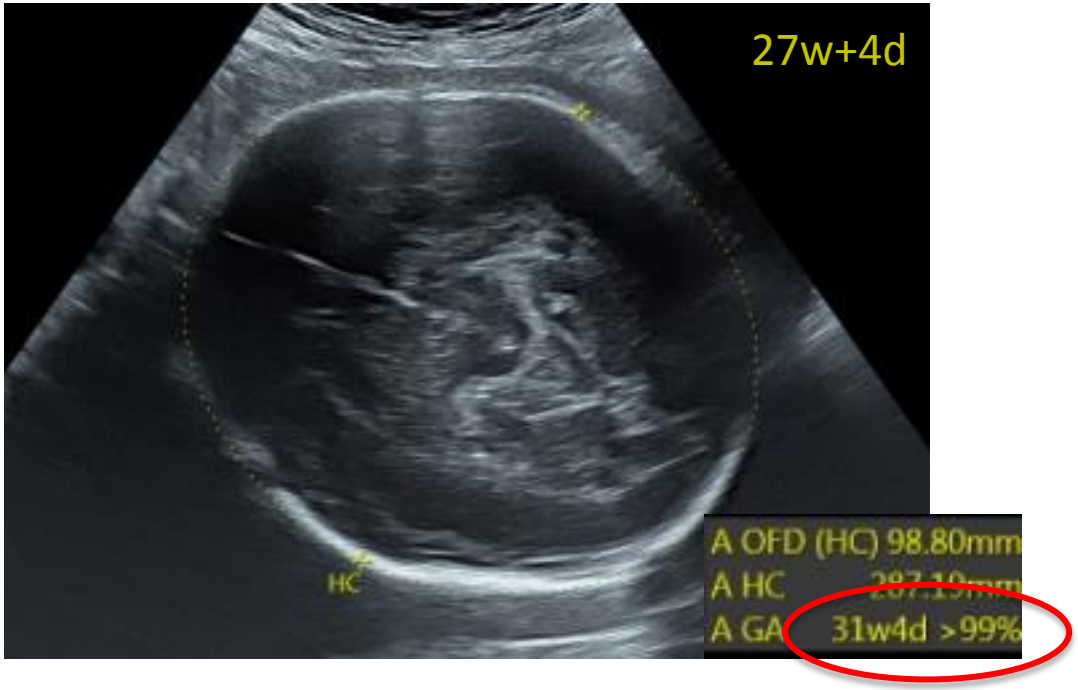


Incidence moderate/severe mental retardation:
HC -2-3 SD below mean: 10-30%
HC -3-4 SD below mean: 50-60%
HC <-4 SD below mean: nearly 100%

Malinger et al., **Reproductive Biology and Endocrinology** , 2003

Makrosefali

Makrosefali

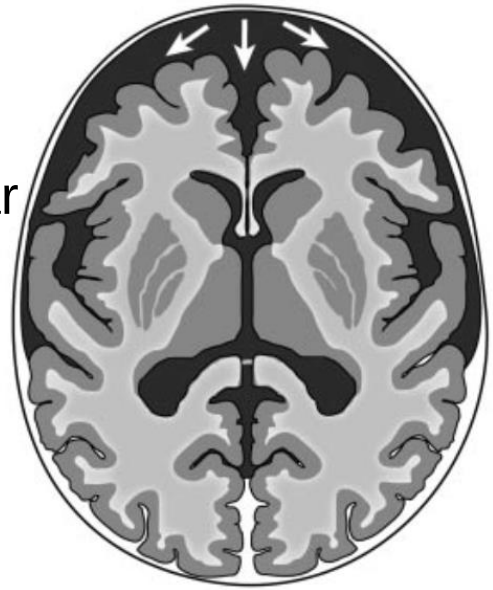


Tanım: HC >98. persantil veya ortalamanın >+ 2 SD

Nadir; sıklığı ?

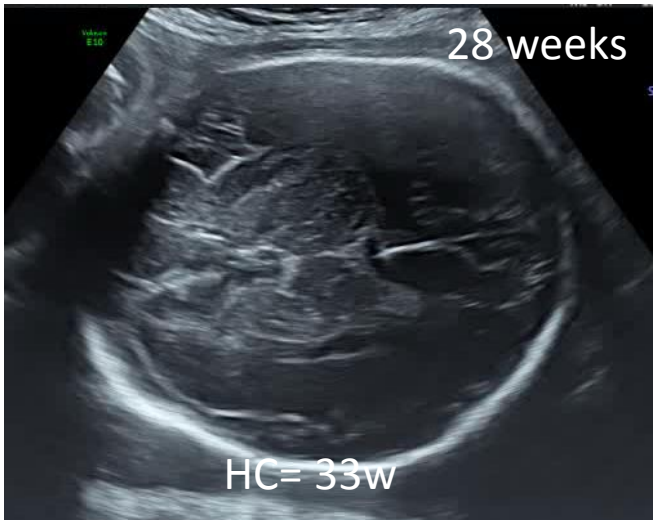
Tümör, subdural hematom, genişlemiş subaraknoid boşluk veya hidrosefali yokluğunda makrosefali ile makroensefali (veya megalensefali) eş anlamlıdır.

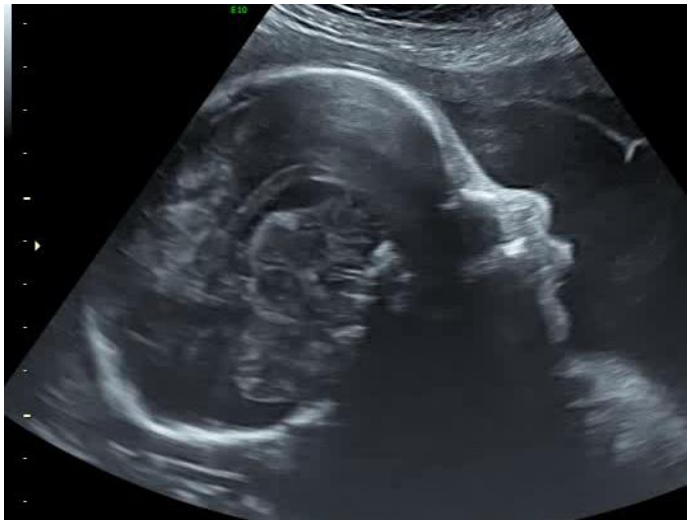
Benign familial makrosefali

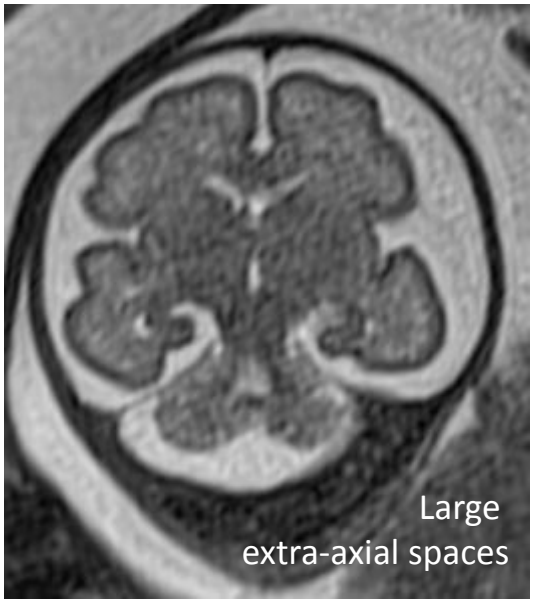


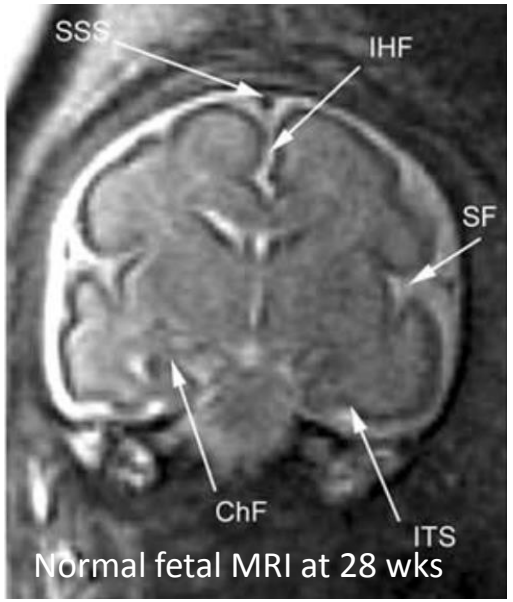
- Frontal subaraknoid mesafe geniş
  - özellikle interhemisferik fissür frontal hemisferler birbirinden uzaklaşacak şekilde geniş, frontal loblar atrofik görünümde
- Lateral ventriküller normal veya hafif dilate
- Patofizyoloji:
  - BOS emiliminin yetersiz (İnmatür villus)
  - Kafatasının beyin dokusundan daha hızlı büyümesi
- Termde HC üst sınıra yakın persantillerde; doğum sonrası artarak 2. yılın sonunda >+2 SD
  - **Genelde OD**; OR veya sporadik de olabiliyor
  - **Erkeklerde kızlara göre 4 kat daha sık**
- **Prognoz genelde çok iyi**; olguların küçük bir kısmında nörolojik gelişim bozuk olabilir; familial makrosefali öğrenme güçlüğü için bir risk faktörü olabilir

Vaka





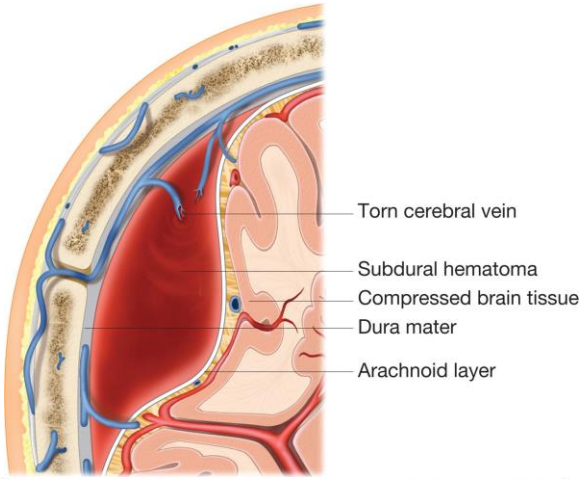


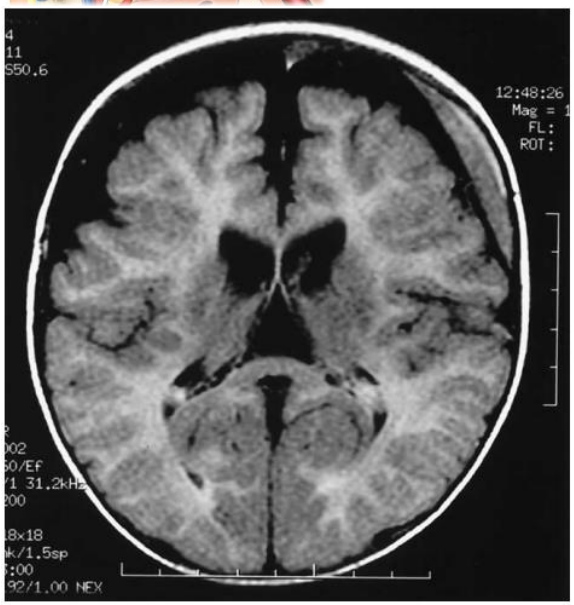


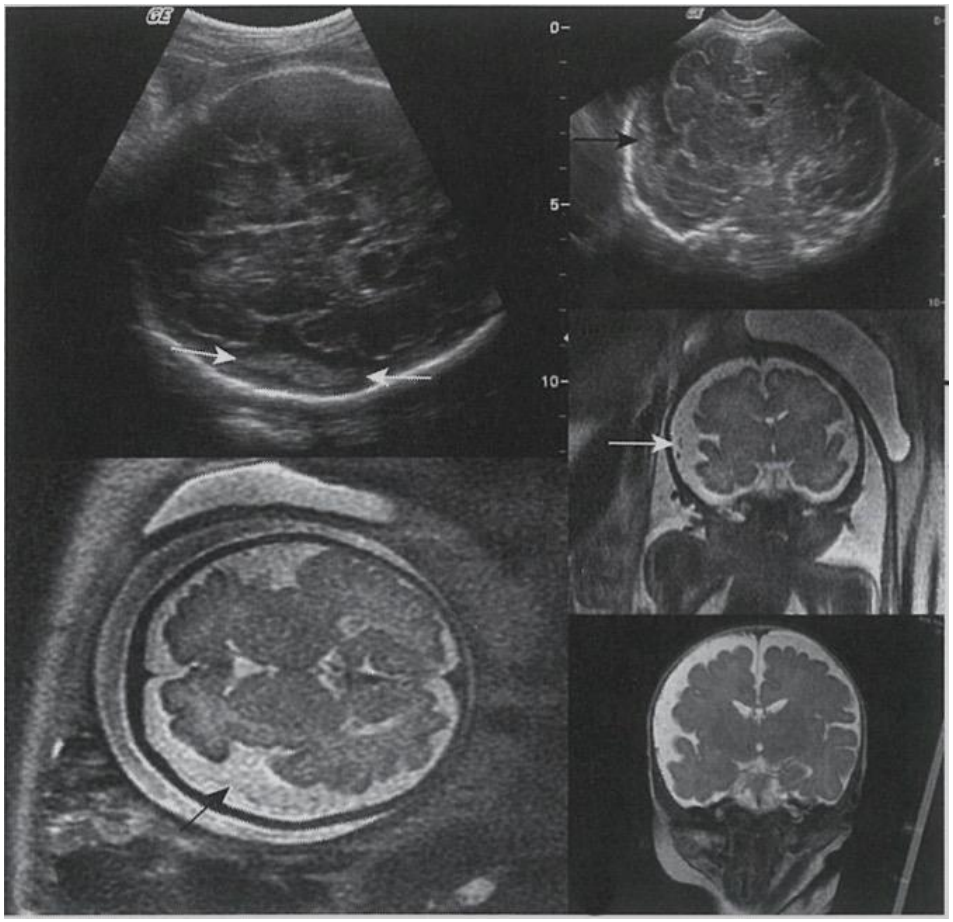
Tanı kriterleri (DeMyer):

- Kraniofasial, nörokütanöz veya başka somatik anomalilerin yokluğu
- Beyin radyolojik olarak normal
- 1. Derece akrabaların (anne,baba,kardeş) birinde makrosefali

Subdural hematom







Malinger

Ravid S, Maytal J. External hydrocephalus: A probable cause for subdural hematoma in infancy. Pediatr Neurol 2003

Etiology - macrocephaly

Genetic types

- Isolated Familial macrocephaly (50%)
- Metabolic types
  - With leukodystrophy
    - Alexander disease
    - Canavan disease
    - Megalencephalic leukodystrophy
  - With organic acidurias
    - Glutaric aciduria, type 1
    - Hydroxyglutaric aciduria
  - With storage
    - Tay-Sachs disease
- Bone dysplasia/hyperplasia
  - Achondroplasia, Thanatophoric dysplasia
- Autism disorder
  - Multifactorial, non-syndromic type
- Hydrocephalus
  - Aqueductal stenosis types
  - Multifactorial, non-obstructive types
- Syndrome associations (many types)
  - With overgrowth
    - Beckwith–Wiedemann syndrome
    - Sotos and Weaver syndrome
    - Simpson–Golabi–Behmel syndrome
    - MCAP (megalencephaly-capillary malformation-polymicrogyria) syndrome
    - Perlman syndrome
    - Costello syndrome
  - With cutaneous findings
    - PTEN hamartoma syndromes
    - Neurofibromatosis, type 1
    - Hemimegalencephaly
  - Neuro-cardio-facial-cutaneous syndromes
    - Noonan syndrome
    - Costello syndrome
    - Cardiofaciocutaneous (CFC) syndrome
    - LEOPARD syndrome
  - With mental retardation
    - Fragile X

Non-Genetic types

- Hydrocephalus
  - Hemorrhage
  - Infections; other causes
- Subdural effusions
  - Post-traumatic and infectious
- Arachnoid cysts

Makrosefali + Makrozomi

Beckwith-Wiedemann

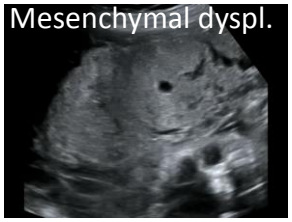
No mental retardation

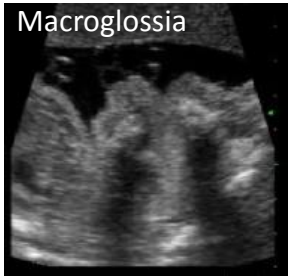
No brain anomalies

Polyhydramnios
Placentomegaly
Omphalocele
Nephromegaly
Cardiomegaly, CHD

+/- increased MSAFP

85% sporadic, rest OD





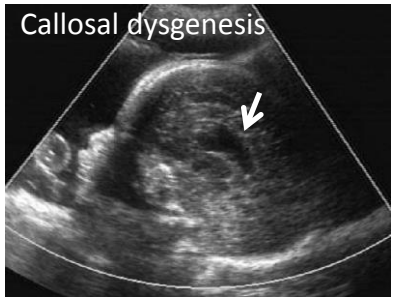
Offer karyotyping and FISH for 11p15 region

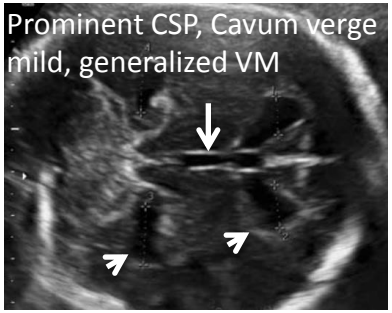
Sotos

variable mental deficiency

Polyhydramnios

+Brain anomalies:





(+)triple test for T21 (⇧hCG)

95% sporadic, rest OD

Offer karyotyping and FISH for 5q35 region
NSD1 sequencing
MRI

Simpson-Golabi-Behmel

Normal intelligence possible
Usually mild-severe MR

Polyhydramnios
Subtle brain anomalies
- Ventriculomegaly
Postaxial polydactyly
Diaphragmatic hernia
Macroglossia
CHD

+/- increased MSAFP

X-linked recessive

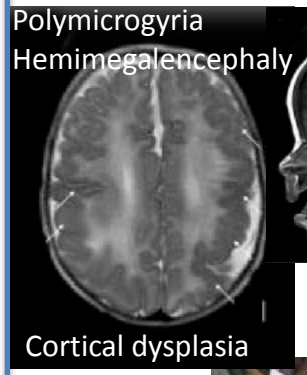
Offer karyotyping and GPC3 sequencing at Xq26
Examine mother for subtle findings (accessory nipples etc)

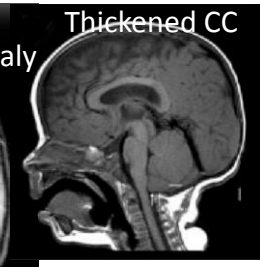
MCAP

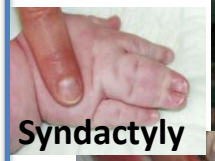
(megalencephaly-capillary malformation-polymicrogyria)

All cases have MR seizures

Prominent brain anomalies



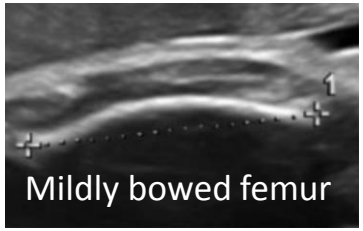


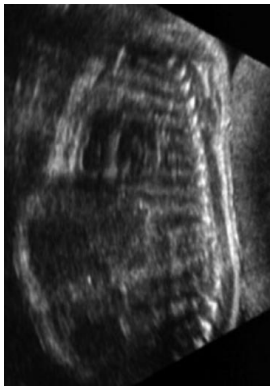


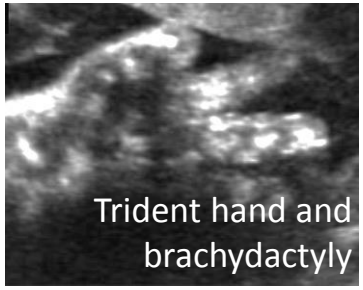
Mosaic mutations in the oncogene PIK3CA are causative (3q26-32)

Genetic testing available on research basis

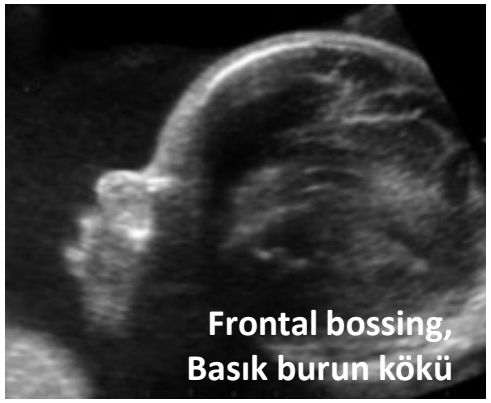
Akondroplazi







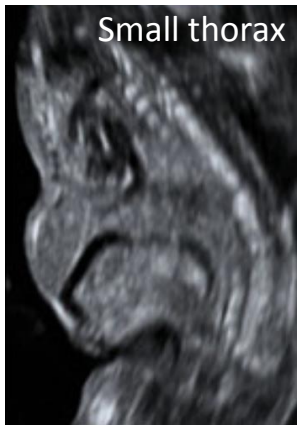
Rölatif makrosefali

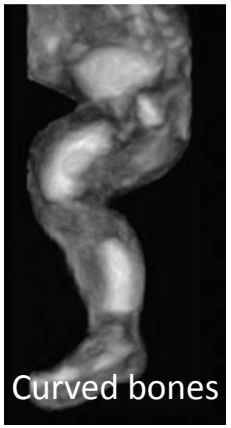


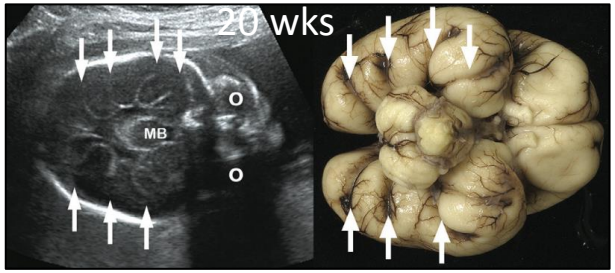
Mutation in FGFR3
4p 16.3

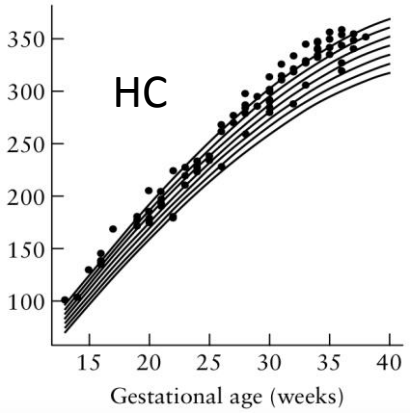
Otozomal Dominant

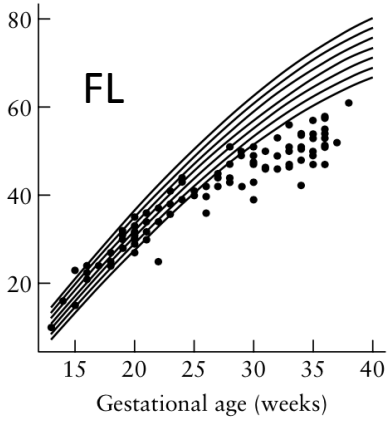
Thanatoforik displazi

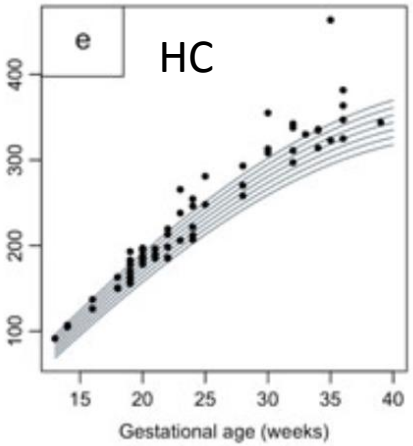


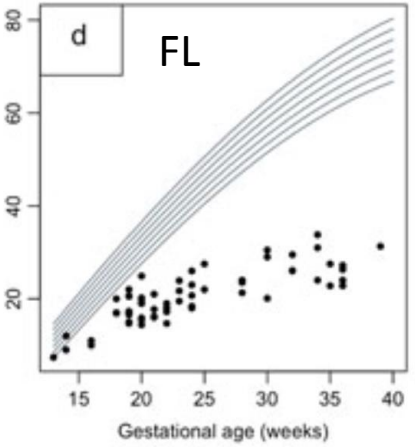












PTEN hamartoma tümör sendromları

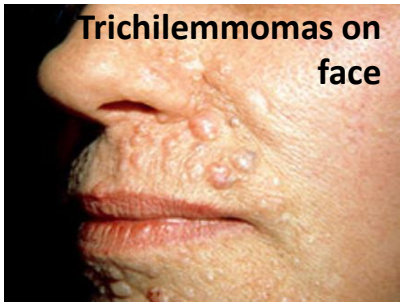
nadir | OD | PTEN-geni

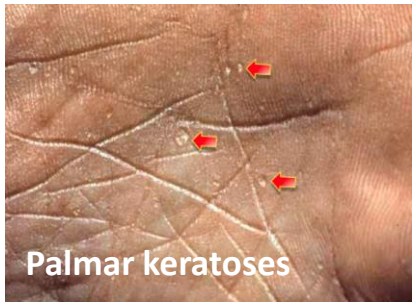
mTOR growth signaling system

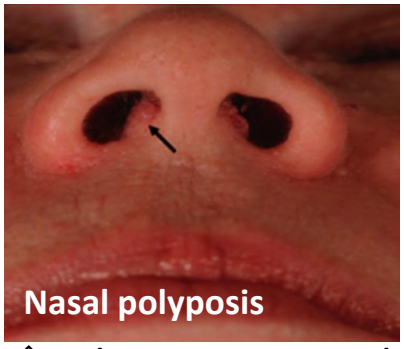
Nörofibromatozis-tip1

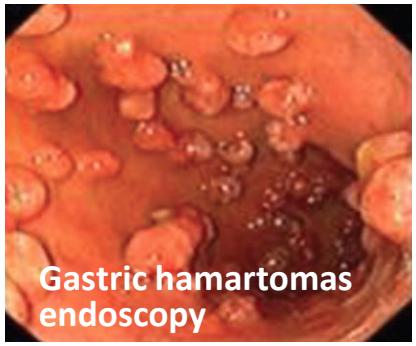
NF1-geni | OD | 1/3000

Cowden sendromu









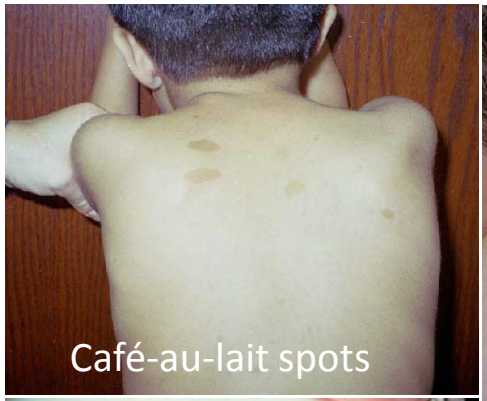
⇧risk: meme, tiroid, endometrium ca

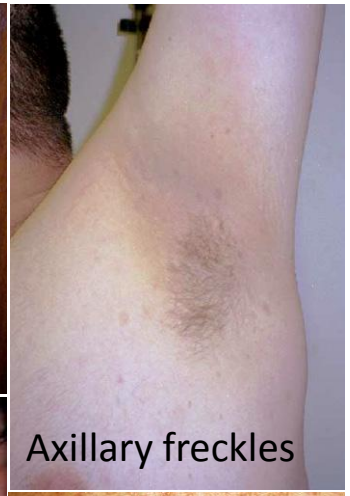
Lhermitte–Duclos hastalığı
Cowden sendromunun variantı:
+ serebellumda displastik gangliositom

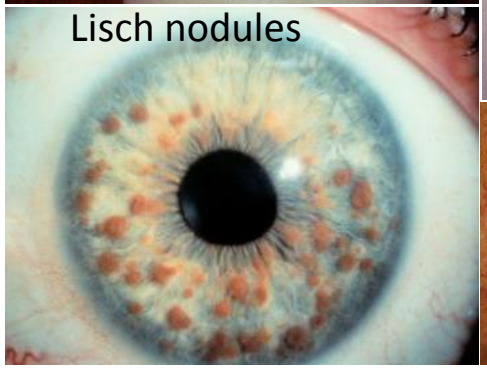
Bannayan–Riley–Ruvalcaba sendromu
nöromotor gelişim geriliği, lipomlar, hemanjiomlar, glans peniste pigmente maküller, lipid storage myopathy

?

Makrosefali





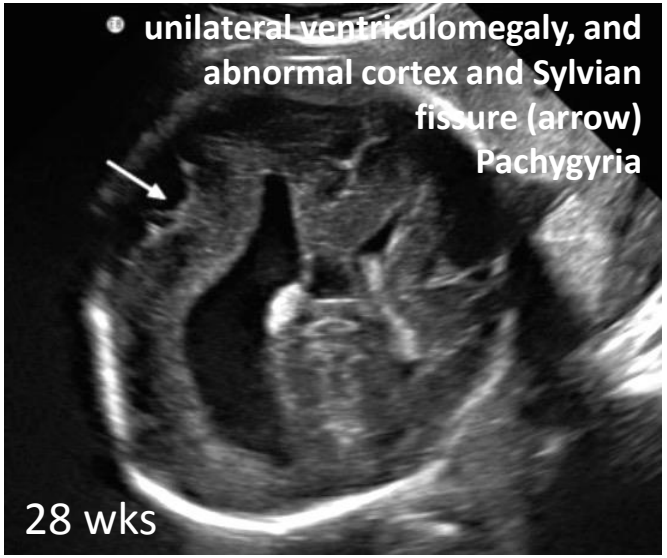


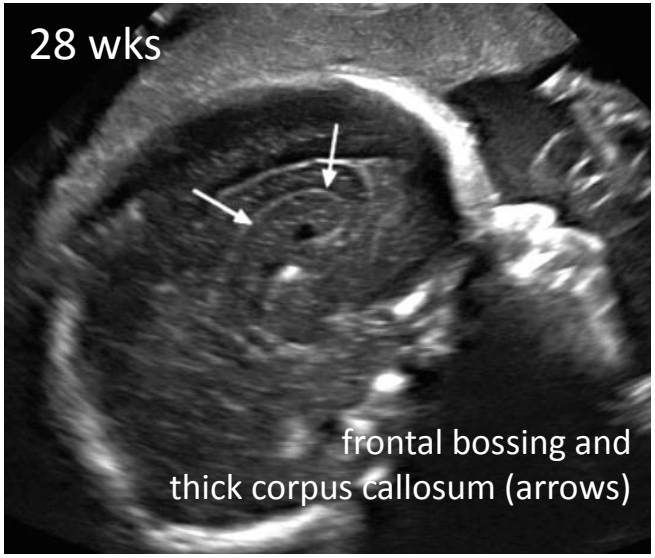
macrocephaly in late gestation
Prenatal findings nonspecific:
+ ventriculomegaly
shortened long bones
polyhydramnios

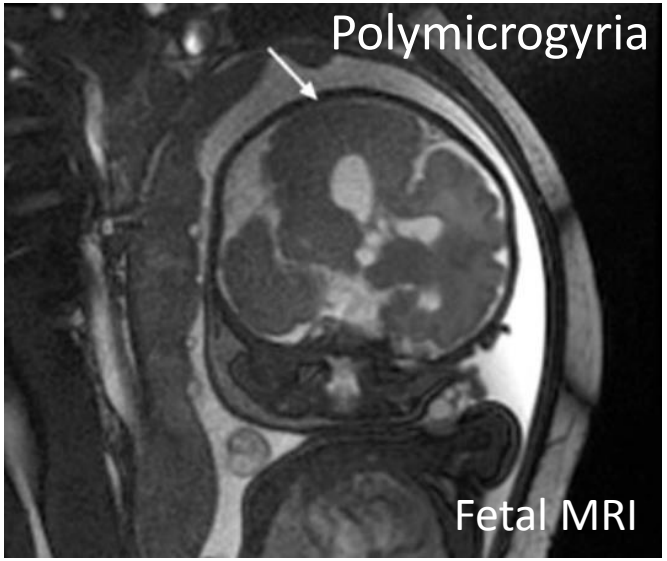
Hemimegalensefali

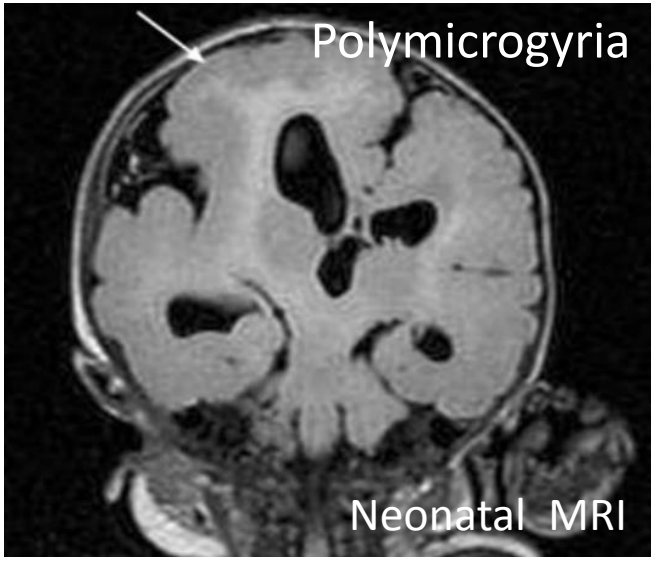
- Hemimegalensefali bir serebral hemisferin tek taraflı olarak kısmen veya bütünüyle büyümesini ifade eder
- Gross patolojide **pachygyri/agyri ile birlikte genişlemiş lateral ventriküller** izlenir
- **Kortikal displazinin ekstrem formu** olarak kabul edilir
- Prognoz ileri derecede kötüdür; inatcı konvülziyonlar
- **Hemimegalensefali izole olabilir veya nörokütanöz sendromlara eşlik edebilir**:
  - MCAP sendromu
  - Tüberoz skleroz
  - Nörofibromatozis tip-1
  - Lineer epidermal nevüs sendromu (LENS)
  - Klippel – Trenaunay – Weber sendromu

Hemimegalensefali



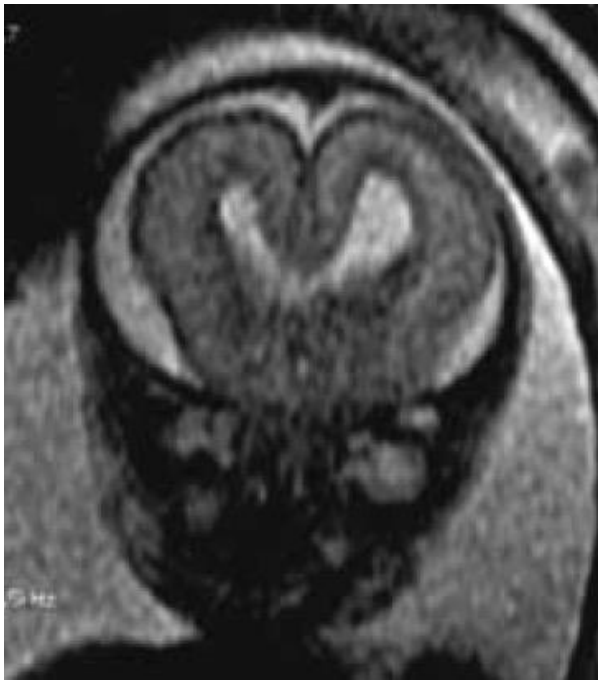




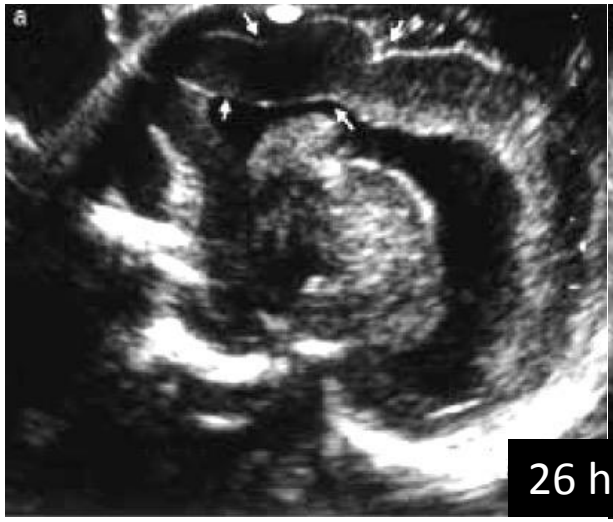


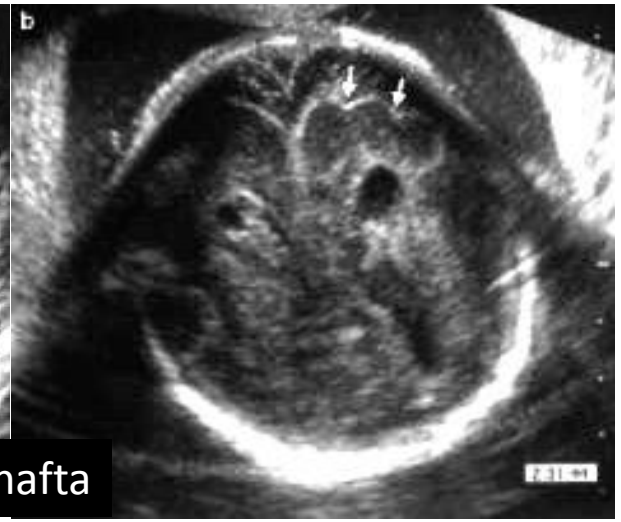
A normal second-trimester ultrasound does not exclude intracranial structural pathology

G. MALINGER*, T. LERMAN-SAGIE†, N. WATEMBERG†, S. ROTMENSCH*, D. LEV‡ and M. GLEZERMAN*



22 hafta: ventriküler asimetri





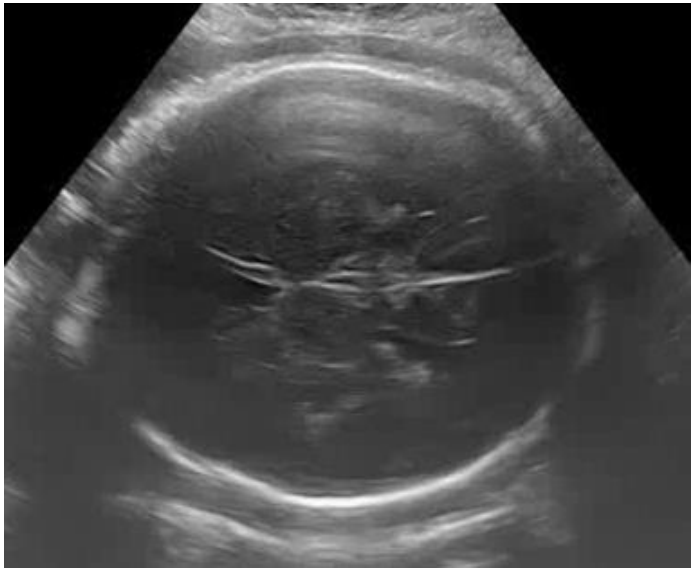
26 hafta

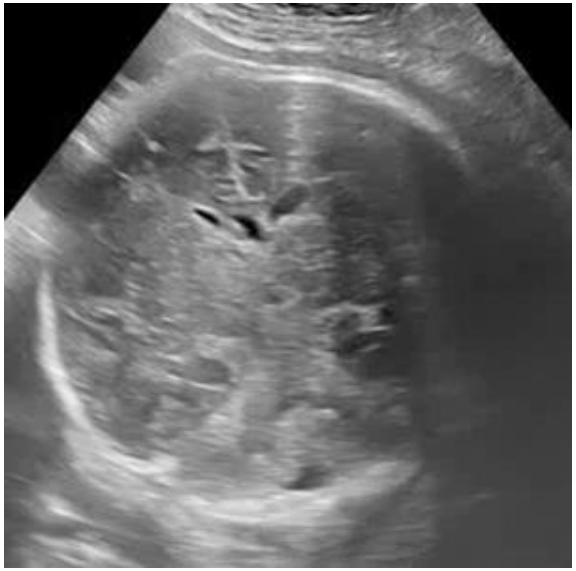
Parasagital kesit:
kalın ve düzensiz oksipital parankim + ventrikülomegali

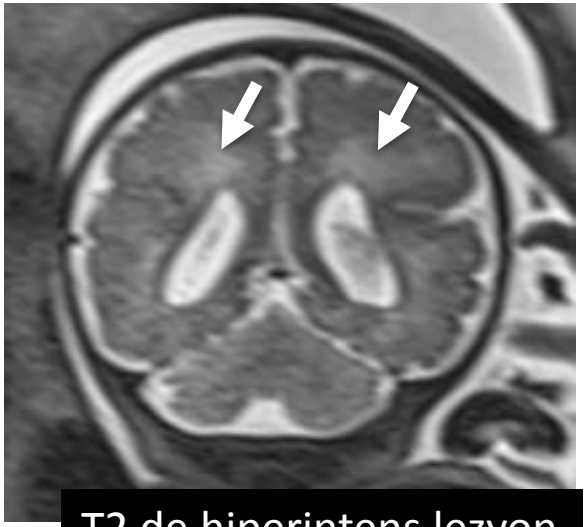
Modifiye koronal kesit:
anormal gyrus ve sulkus

Ultrasound Obstet Gynecol 2002; 20: 51–56

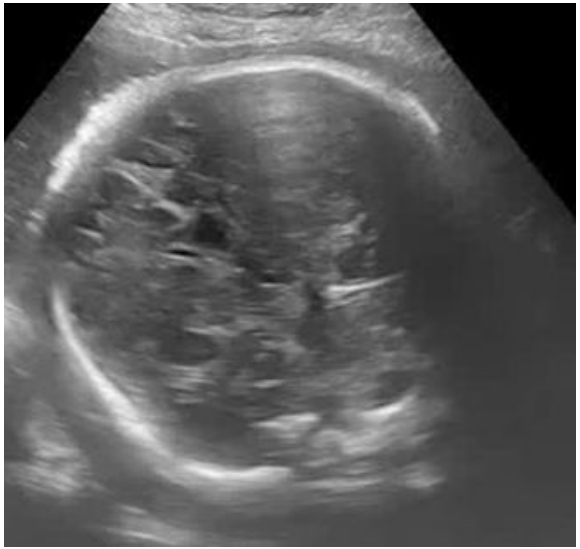
Nörometabolik hastalıklar

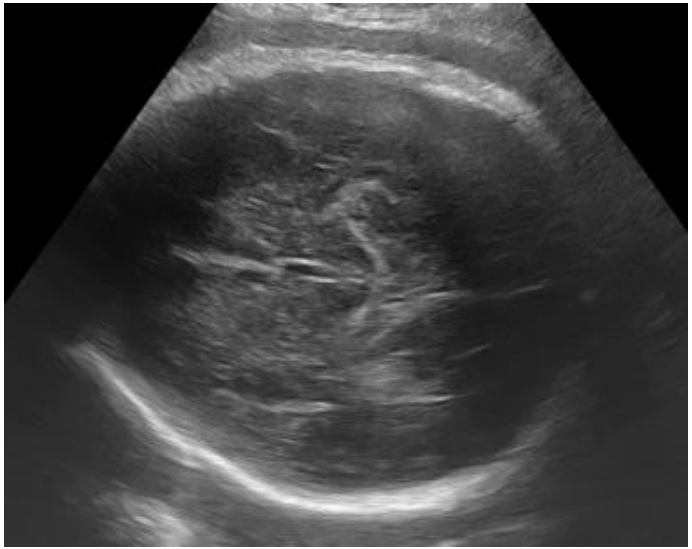


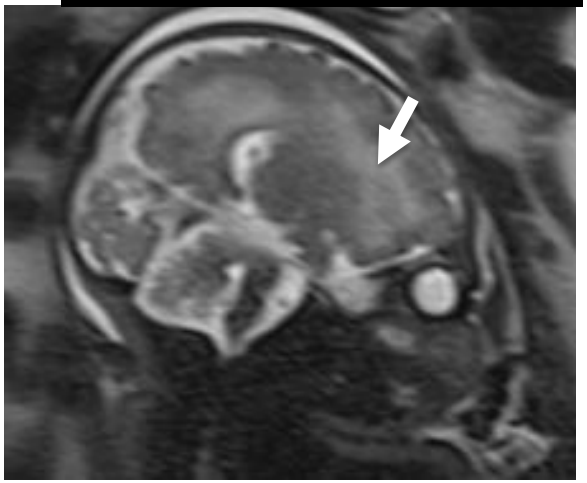




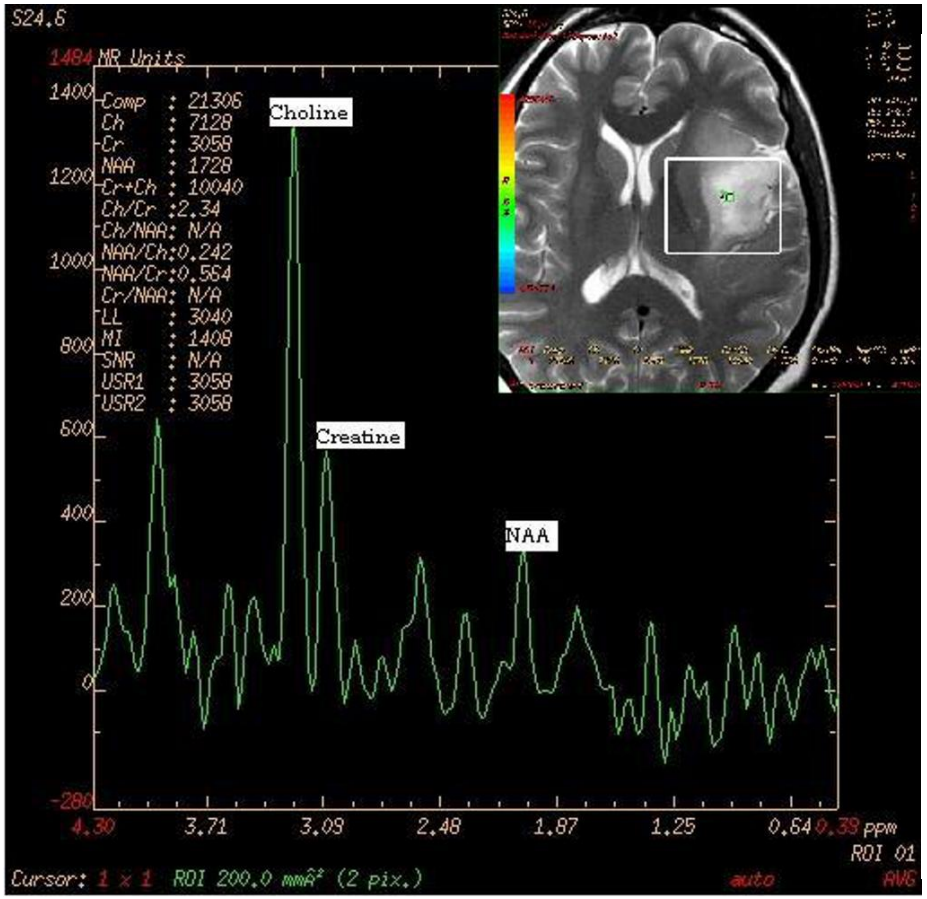
T2 de hiperintens lezyon







MR spektroskopi

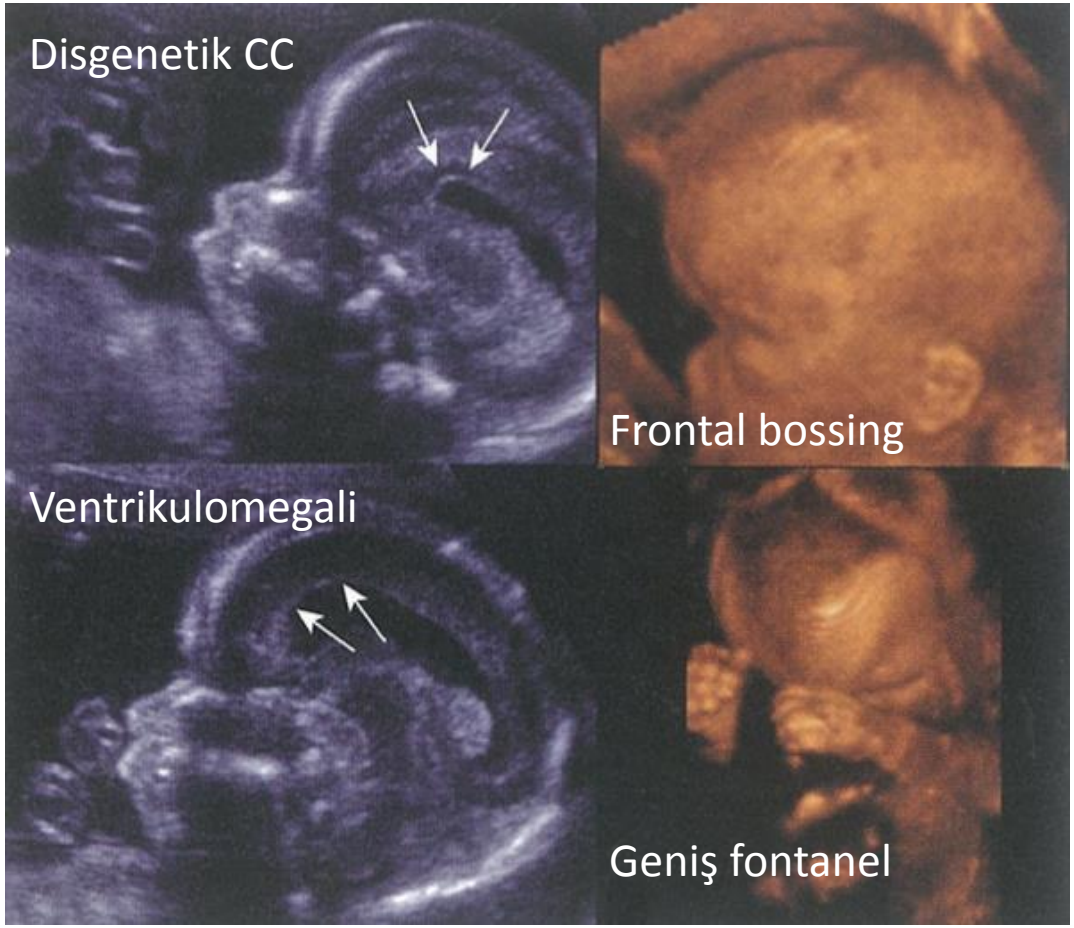


Peaks

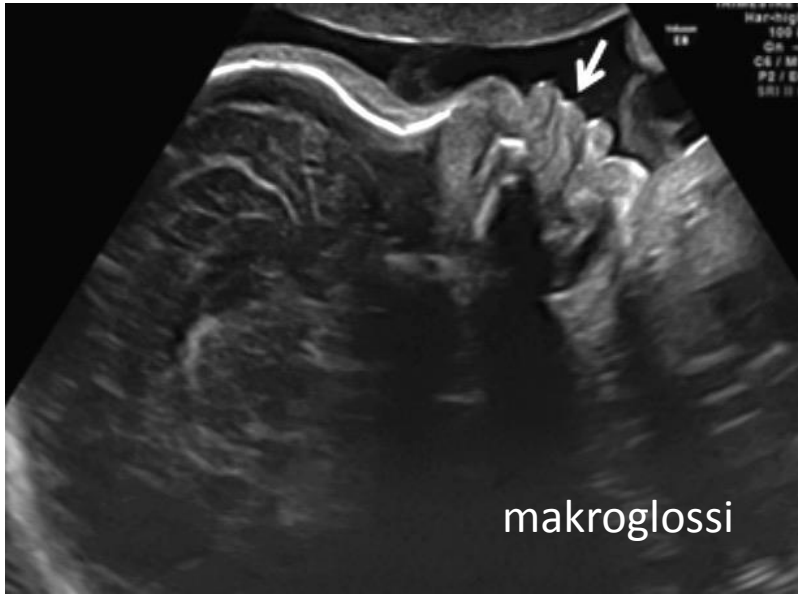
- lactate: resonates at 1.3 ppm
- lipids: resonates at 1.3 ppm
- alanine: resonates at 1.48 ppm
- N-acetylaspartate (NAA): resonates at 2.0
- glutamine/glutamate: resonates at 2.2-2.4 ppm
- GABA: resonates at 2.2-2.4 ppm
- 2-hydroxyglutarate: resonates at 2.25 ppm [6]
- citrate: resonates 2.6 ppm
- creatine: resonates at 3.0 ppm
- choline: resonates at 3.2 ppm
- myo-inositol: resonates at 3.5 ppm
- water resonates at 4.4 ppm

Kromozomal anomali

3q delesyon

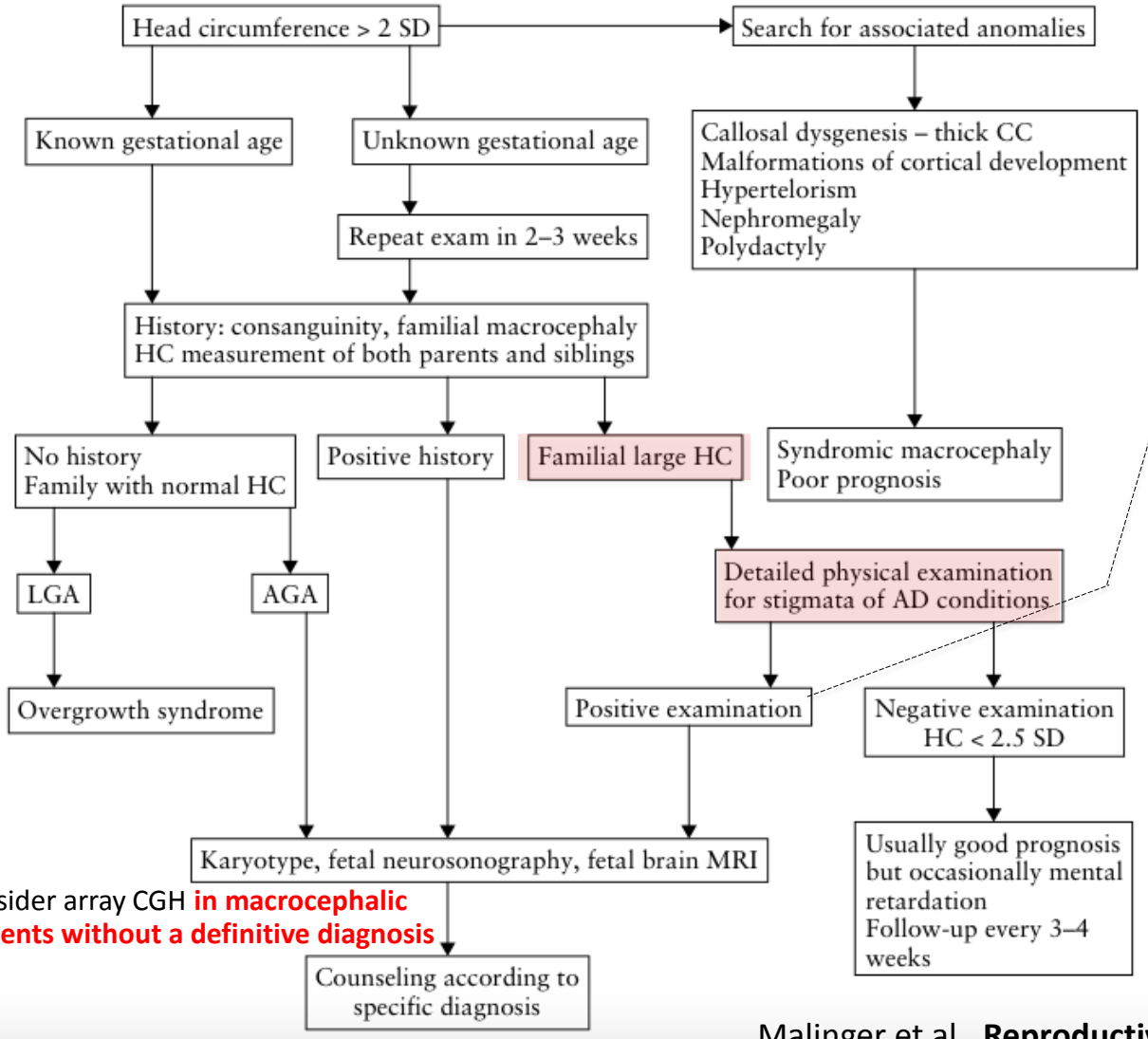


13q31.1 mikrodelesyon



dup 1q21.1 = makrosefali
del 1q21.1 = mikrosefali

Flow chart in patients with suspected macrocephaly



careful medical history of the affected parent regarding

- **neurological problems**
- **developmental milestones**
- **skin abnormalities**
- **propensity for the development of tumors**

consider array CGH **in macrocephalic patients without a definitive diagnosis**

Malinger et al., **Reproductive Biology and Endocrinology** , 2003

Makrosefali - prenatal yönetim

- Detaylı ultrason incelemesi (+ Nörosonografi)
  - HC> +2.5-3 SD ve ek anomali sendromik makrosefali lehine; prognoz kötü
    - **Fetal biometri:** iskelet displazisi veya overgrowth sendromları
    - **MSS:** korpus kallosum disgenezis; kortikal gelişim anomalileri
    - **Sistemik:** polidaktili, vasküler anomaliler (hemangiomlar), ekstremite, hipertelorizm
  - İzole HC +2–2.5 SD; prognoz genelde iyi; öğrenme güçlüğü, otizm, geç nöromotor gelişim olabilir.
- Fetal MRI
- Genetik danışma
  - Familial makrosefali
  - OD geçiş gösteren hastalıkların klinik bulguları (cilt muayenesi, endokrin testler, nöromotor gelişim basamakları)
  - Karyotipleme + mikroarray