Tanıyı Siz Koyun
Zorlayıcı Nörometobolik Olguların Çözümlenmesi

27. Ulusal Çocuk Nörolojisi Kongresi

Cengiz Havalı

Doğum Tarihi: 16/05/2019

Muayene Tarihi: 18/06/2025

6 yaşında kız hasta

- İki ay önce bir ÜSYE sonrası başlayan baş ağrısı
- Bir ay önce başlayan huy değişikliği, bağırma, saçma konuşma
- İki haftadır yürürken sendeleme, düşme, düştüğü yerden kalkmakta zorlanma
- Son 1 haftadır yürüyememe, idrar ve gaita kaçırma,

- PRENATAL: NST bozukluğu: +
- NATAL
- Doğum Ağırlığı:1500 gram
- Doğum haftası: 34
- Sezaryen: +
- POSTNATAL
- Komplikasyon: -
- Doğar Doğmaz Ağlamış
- Küvöz İhtiyacı: 40 gün
- Sarılık: yok

- Motor Gelişim
- Desteksiz oturabilme: 7 ay
- Yürüme: 1 yaş

- Dil gelişimi
- Tek kelimeler: 1 yaş
- Cümle kurma: 2 yaş

Kardeşleri sağlıklı

3 Abortus

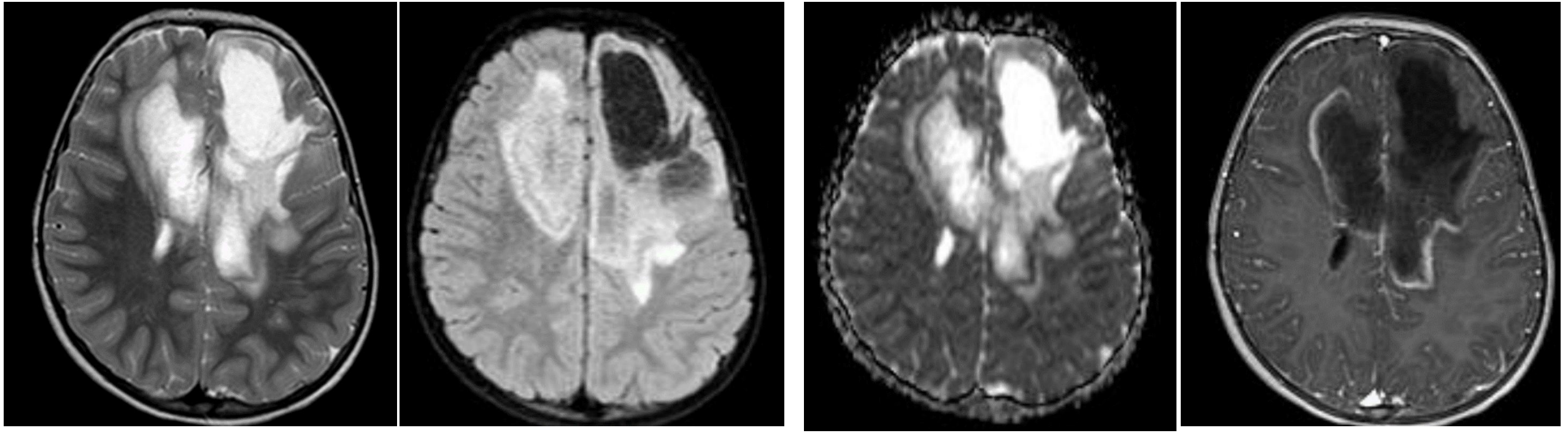
Akrabalık: -

Ailede Hastalıklar: Yok

- Bilinç açık, komutlara uyumu yaşına göre geri
- Pupiller izokorik, DIR /IDIR:++/++
- Göz hareketleri her yöne serbest, pitozis yok
- Fasiyal asimetri yok
- Kas gücü: 4 ekstremite spontan eşit hareketli
- Oturabiliyor, yürüyemiyor
- Tonus doğal
- DTR canlı, klonus ++
- HSM yok, ciltte leke yok

- **Olguyu özetleme**
- Altı yaşına kadar motor, bilişsel ve dil gelişimi normal olan
- Son iki ay içinde ÜSYE sonrası başlayan baş ağrısı olan
- Son 1 ay içinde tüm gelişimsel alanlarda gerileme olan hastanın muayenesinde
- Bilinç açık, komutlara uyumu yaşına göre geri
- Oturabiliyor, yürüyemiyor
- DTR canlı, klonus ++

5.6.2026



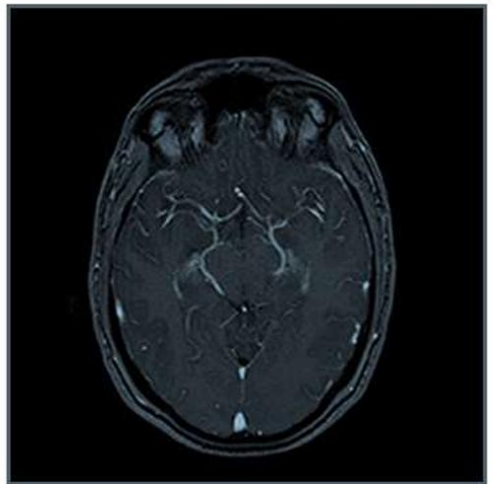
Siz olsaydınız hangi tanıyı düşünürdünüz?

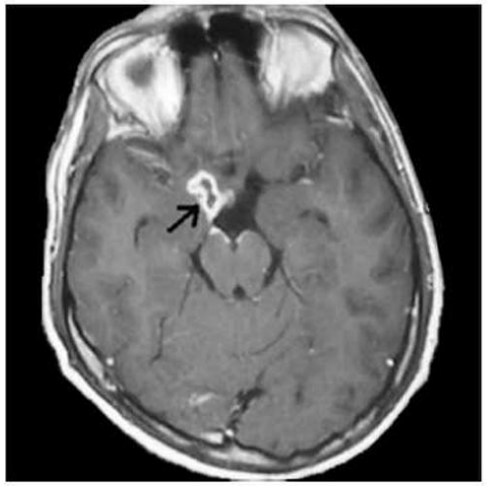
Enfeksiyonlar?

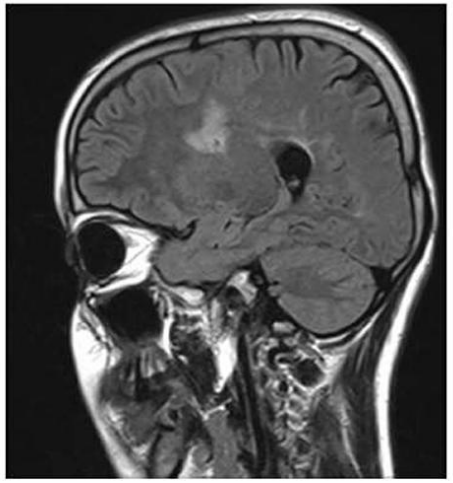
- Ateş yok
- Belirti ve bulgular iki aya yayılmış
- Meninks irritasyon bulguları yok

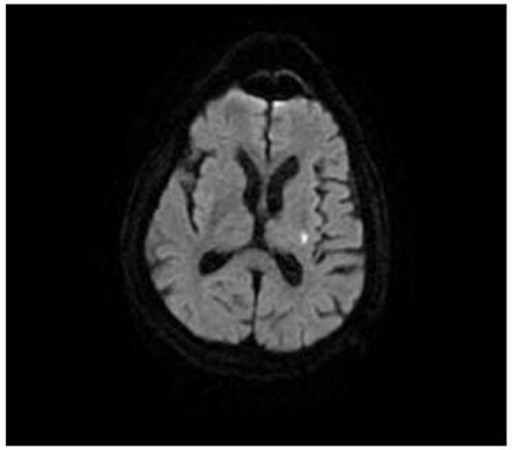
- Neurobrusellozis?
- Nörolojik tutulum menenjit, meningoensefalit (akut veya kronik), intrakraniyal hipertansiyon, sinüs trombozu, radikülit, periferik nöropati, miyelit ve ensefalit, kraniyal nöropatiler, psikiyatrik belirtiler şeklinde ortaya çıkabilir

Nörobrusellozis







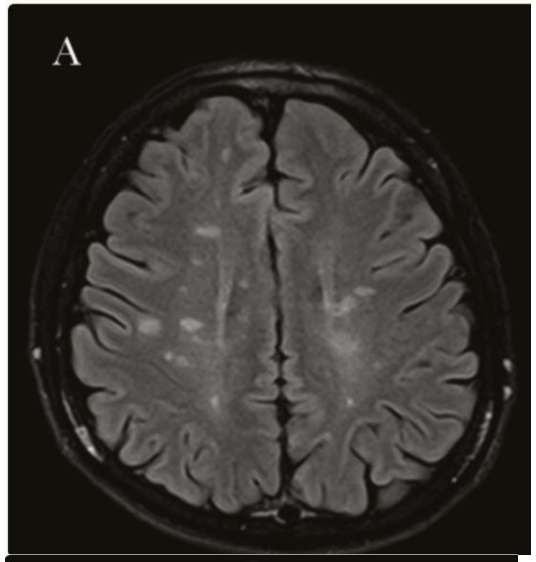


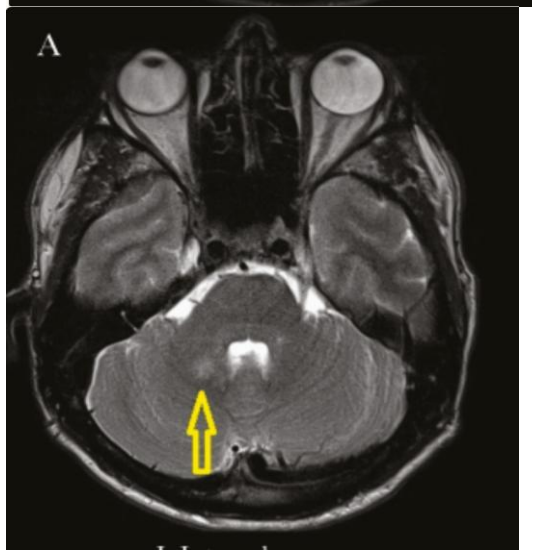
- 119 pediatrik nörobruselloz
- En sık görülen tablo, ensefalitli veya ensefalitsiz menenjitti (n = 79, %71,2).
- Pediatrik popülasyonda kraniyal nöropatilerin yüksek prevalansı (n = 22, %20,7) gözlendi ve bunların en yaygını abdusens felciydi (n = 9, %8,1).

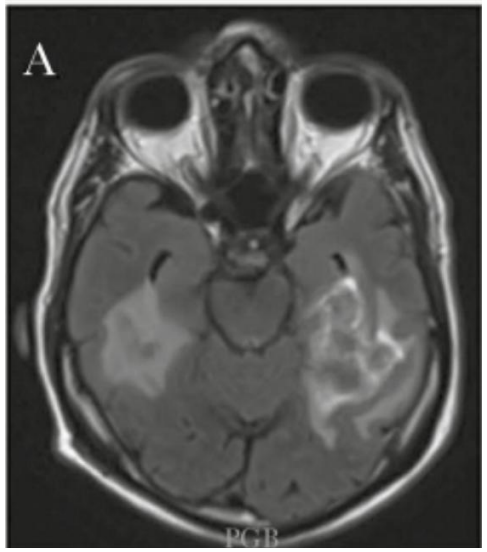
Noroboreliozis?

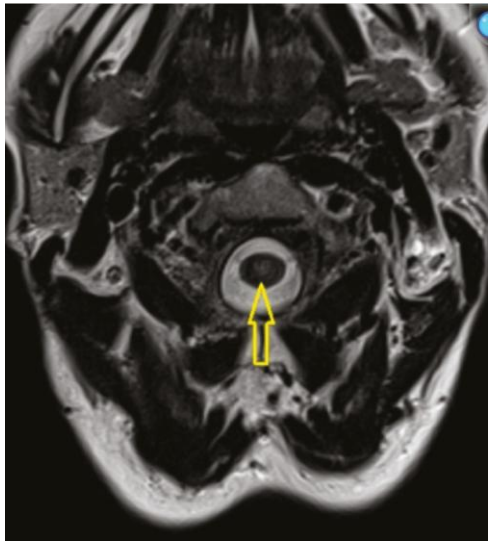
Tablo I- Nöroborrelyozda Klinik Tablolar*

Evre	Klinik Tablo
Erken Disseminasyon Evresi (Evre 2)	Menenjit Kraniyal nörit Fasiyal paralizi Motor veya sensoriyel radikulonörit Ensefalit, ensefalomiyelit Transvers miyelit Mononöropati multipleks Akut brakiyal, lumbosakral pleksopati Optik nörit, korioretinit, retinal vaskülit SSS vasküliti Psödotümör serebri
Geç Dissemi-nasyon Evresi (Evre 3)	Kronik ensefalopati Kronik ensefalomiyelit Kronik aksonal polinöropati Radikülopati Brakiyal, lumbosakral pleksopati Mononöropati Mononöropati multipleks Polinöropati Kraniyal nöropati Spastik paraparezi SSS vasküliti Mental değişiklikler Demans









Tüberküloz menenjit?

Akut bakteriyel menenjitlere göre nispeten daha yavaş ilerleyebilse de

Ateş

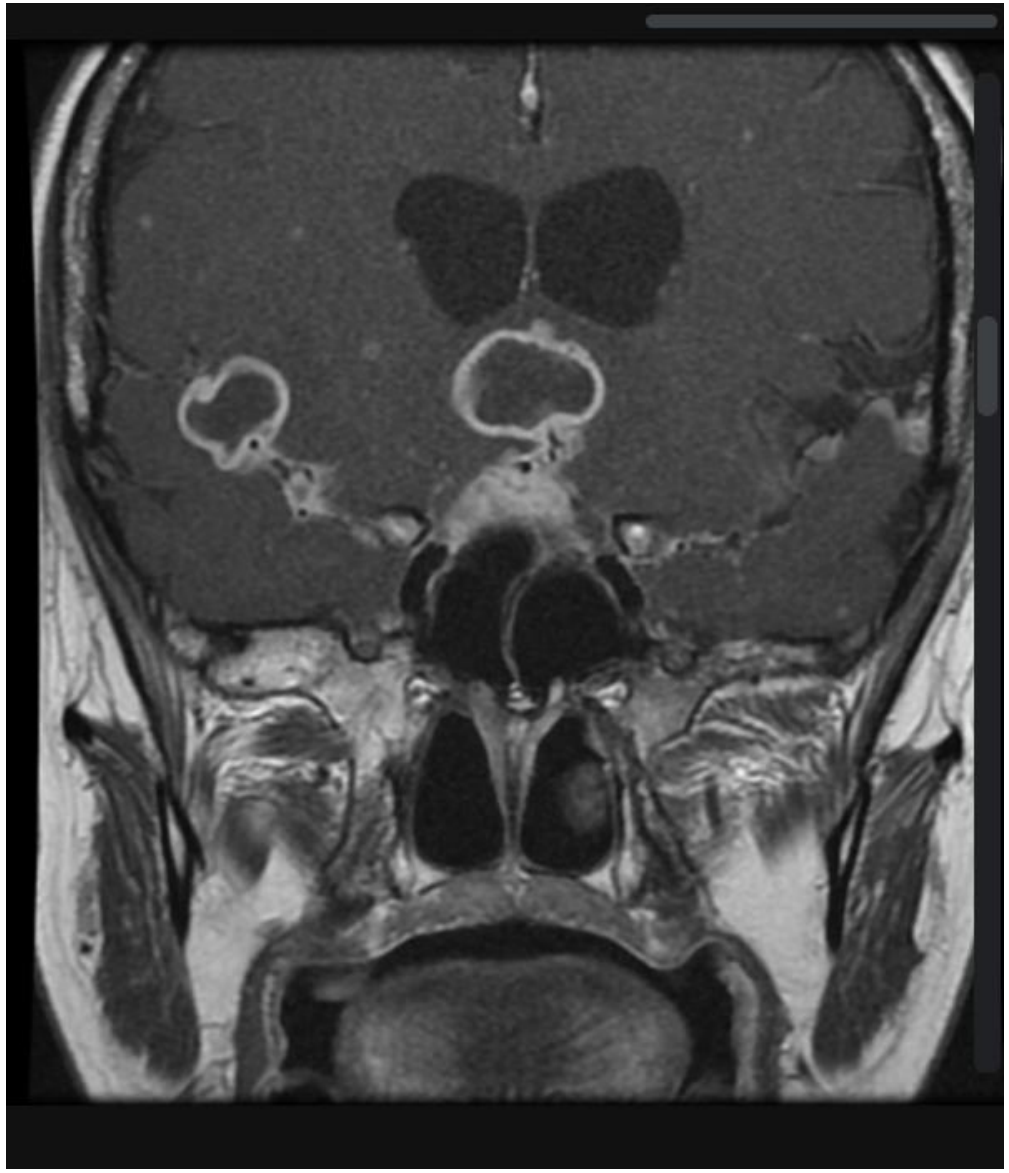
Bilinç bozukluğu

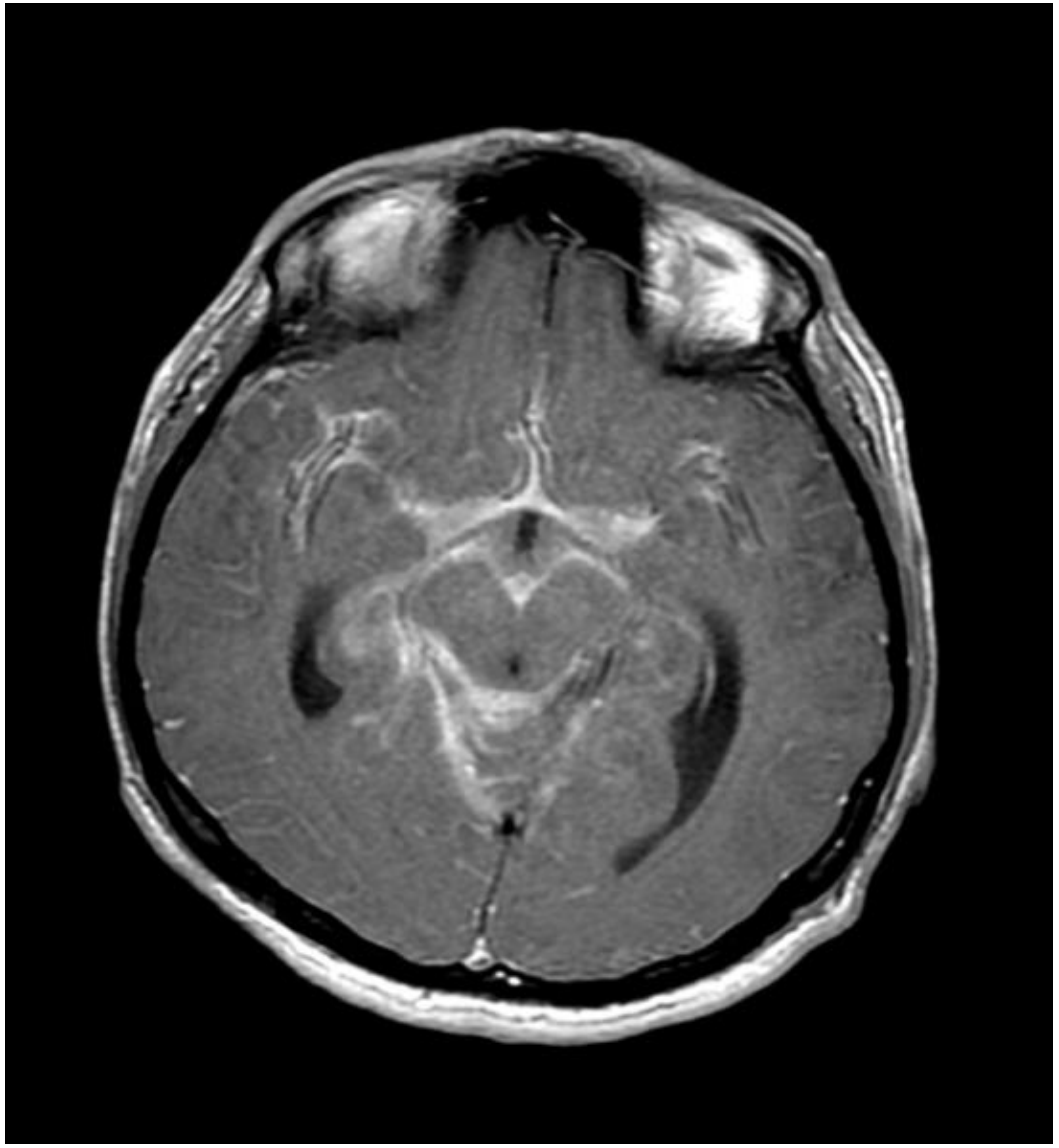
Meninks irritasyon bulguları

1-2 hafta içinde sıklıkla hidrosefali

Daha yıkıcı ve olgumuza göre daha hızlı seyir

TBC menenjit





Yavaş ilerleyen başka bir enfeksiyöz durum ?

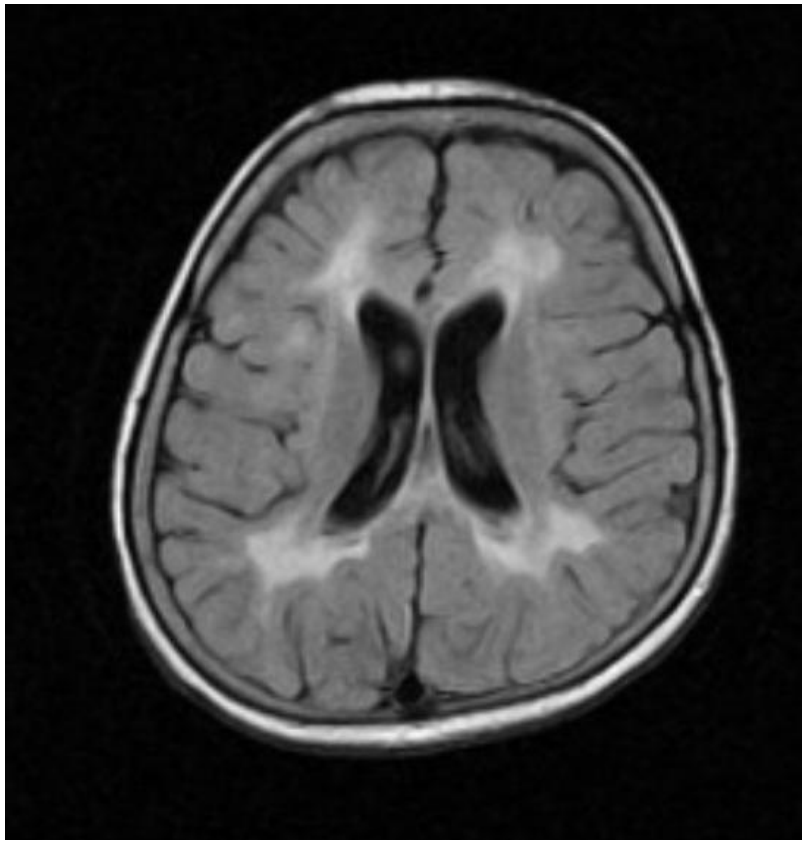
SSPE?

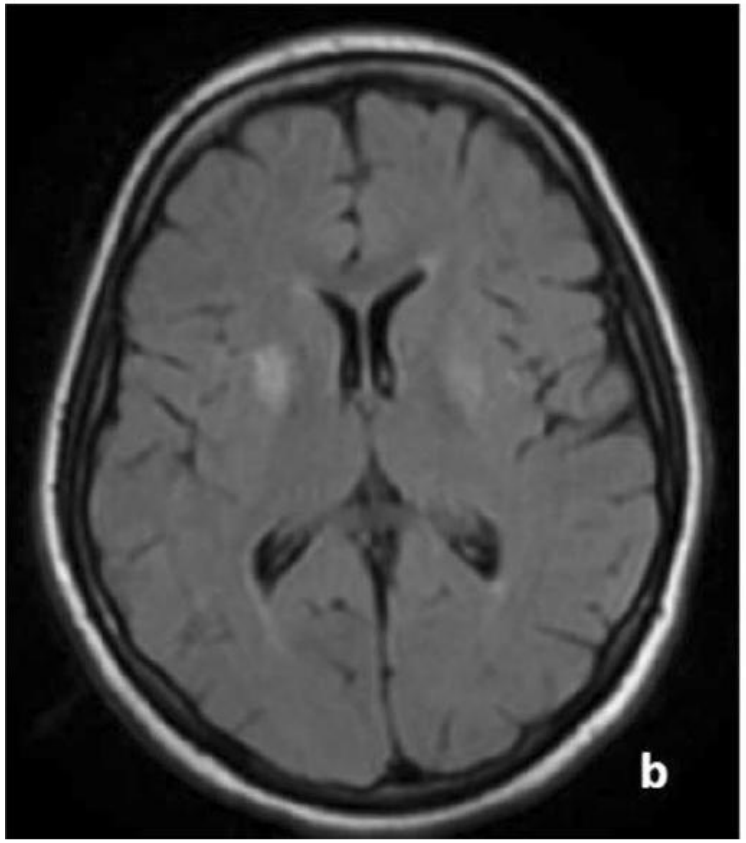
Bilişsel ve motor gerileme

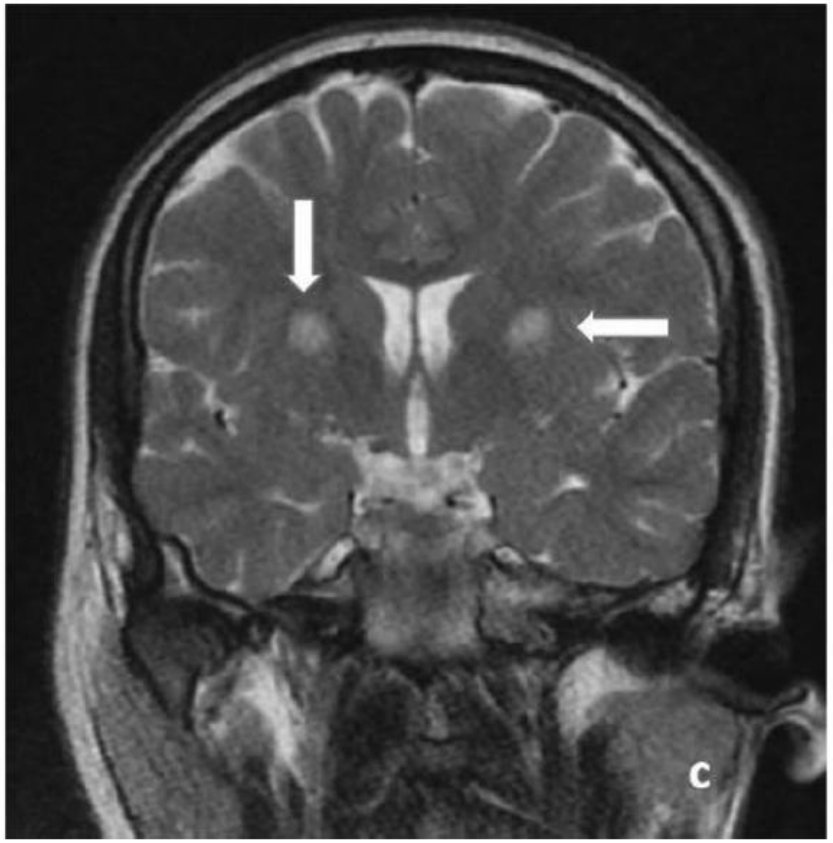
Nöbetler

Normalde olgumuza göre daha uzun zamana yayılmış bulgular beklenir fakat daha hızlı gidişli vakalar ?

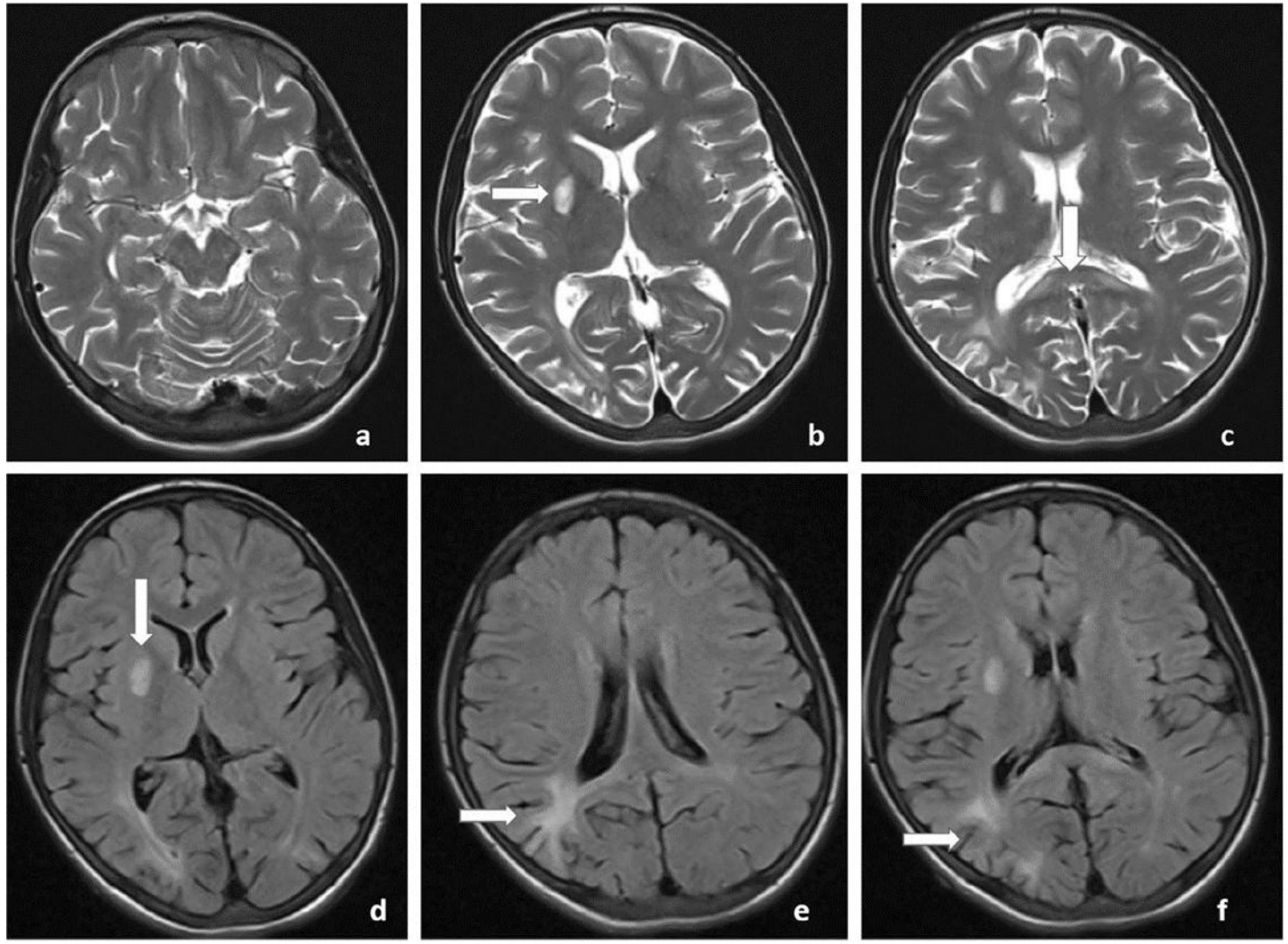
SSPE







SSPE



Otoimmün süreçler?

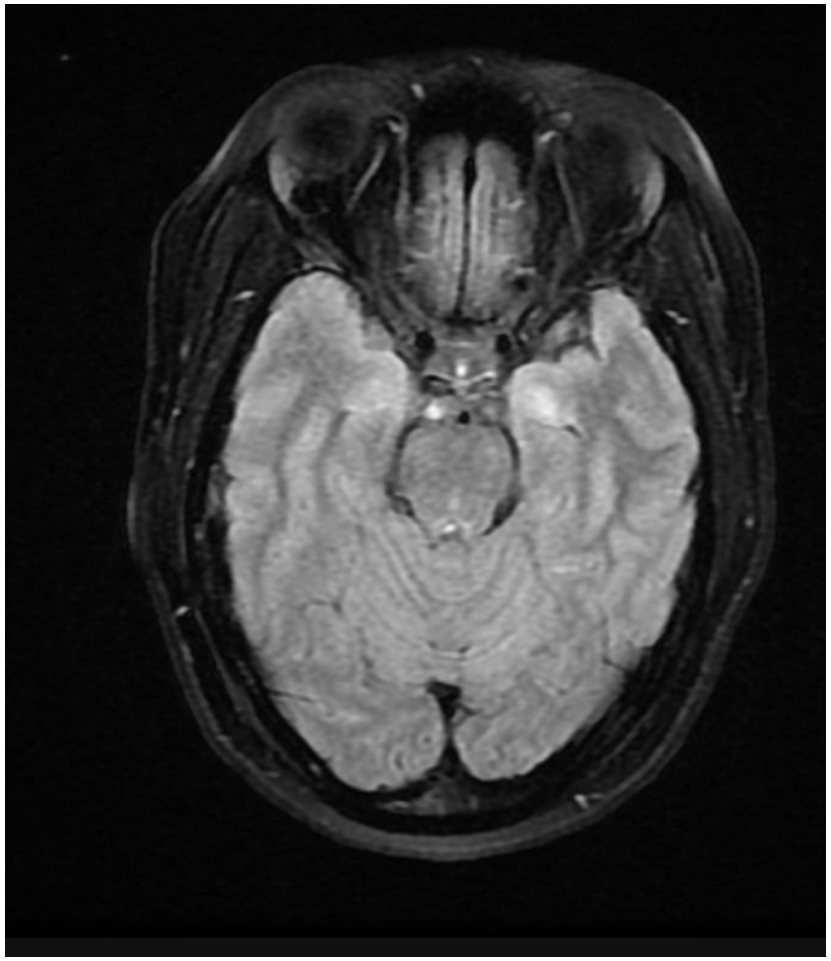
Otoimmün ensefalit ?

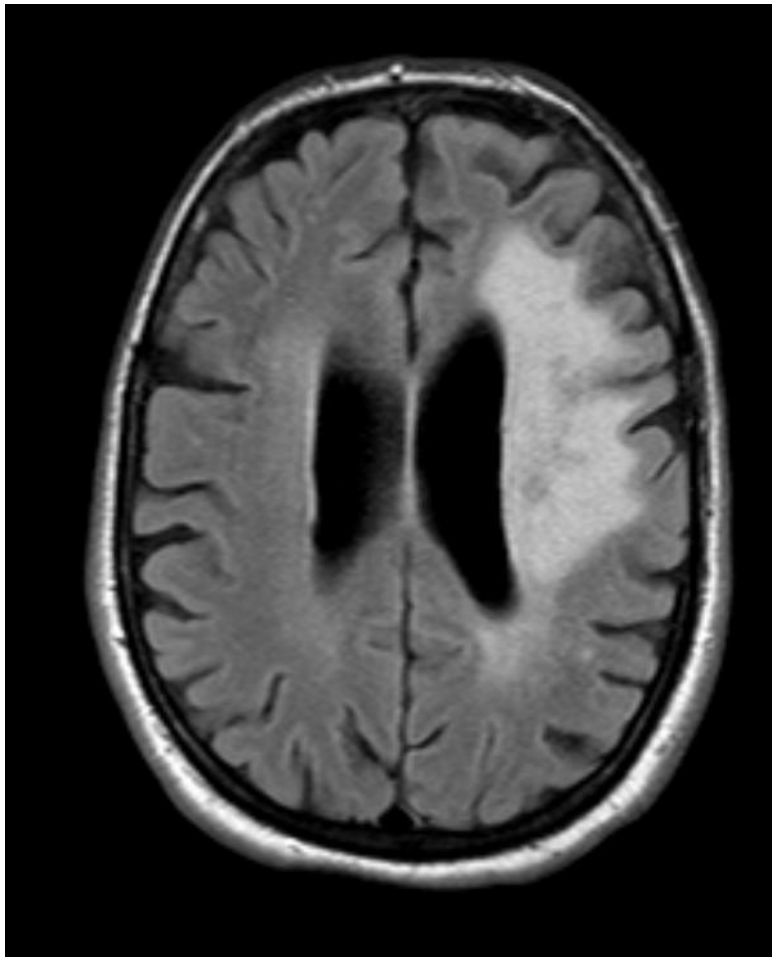
Subakut başlangıçlı motor ve bilişsel bulgular

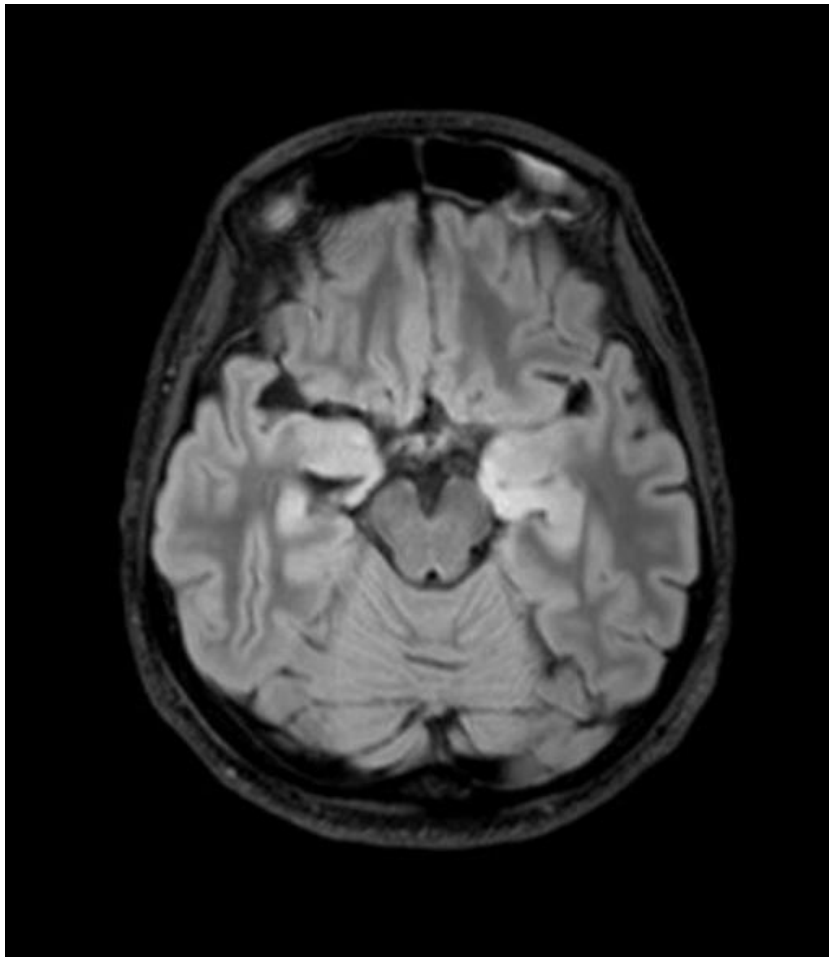
Nöbet

Hareket bozuklukları

OTOİMMÜN ENSEFALİT







Otoimmün ensefalit vakalarının yarısından fazlasında anormal MRG bulguları mevcuttur

En sık görülen tutulum yeri medial temporal loblar ve limbik sistemlerdir ve tipik olarak bu bölgelerde artmış T2/FLAIR sinyal yoğunluğu

Lateral temporal lob, insula, bazal gangliyonlar ve talamuslar dahil olmak üzere daha yaygın bir tutulum olabilir

Limbik ensefalitte difüzyon kısıtlaması nadirdir, kontrast artışı nadirdir ve kanama çok nadirdir

Daha az karakteristik olmakla birlikte merkezi sinir sisteminin hemen hemen her bölümü etkilenebilir

- GABAAR antikor ensefaliti: multifokal kortikal ve subkortikal hiperintensiteler
- D2R antikor ensefaliti: bazal gangliyonlarda anormal lezyonlar
- Vimentin antikor ensefalomiyelit: bilateral serebral kortikospinal yollar boyunca simetrik T2 hiperintensiteleri

Sistemik otoimmün hastalıklar ?

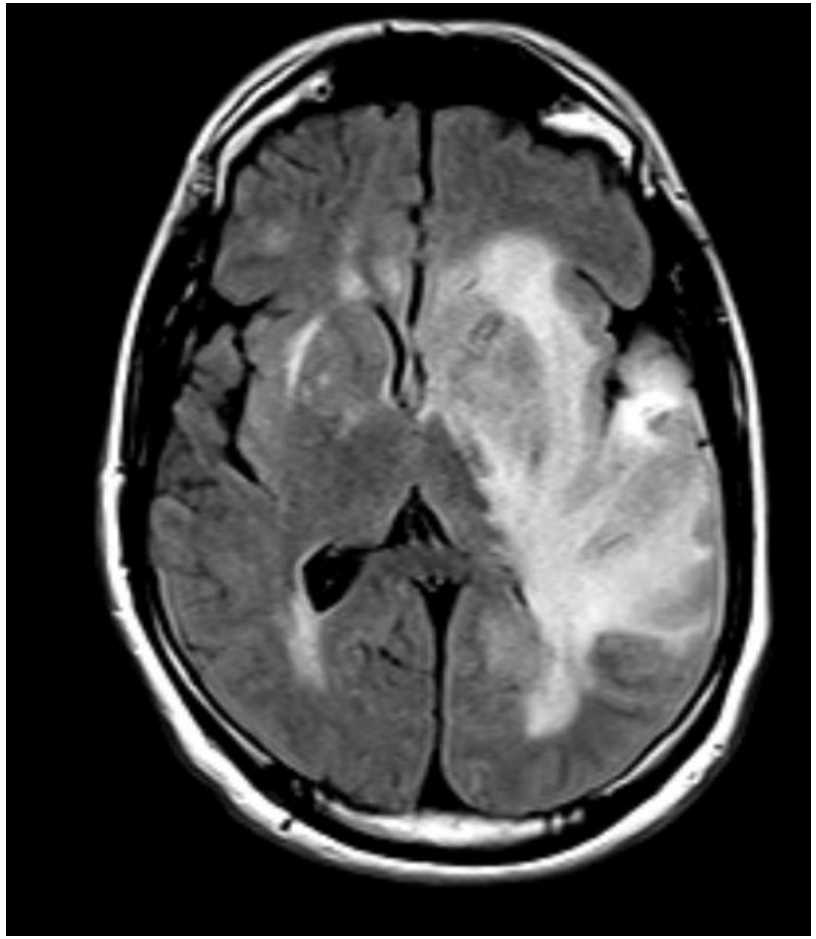
Vaskülitler?

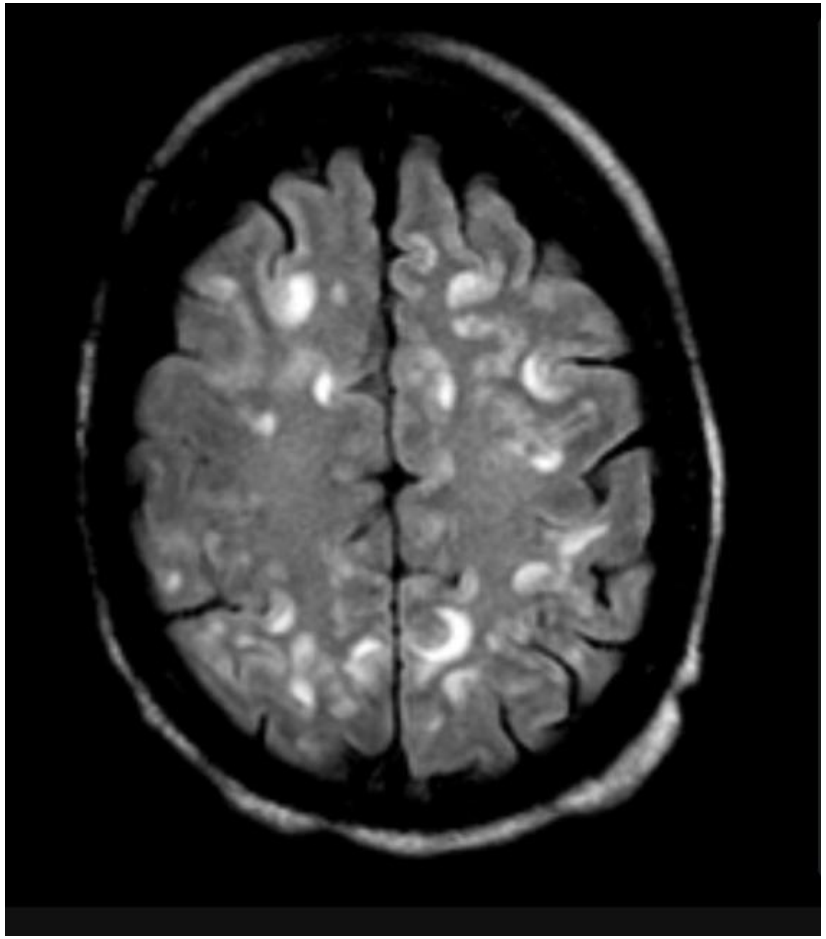
SLE?

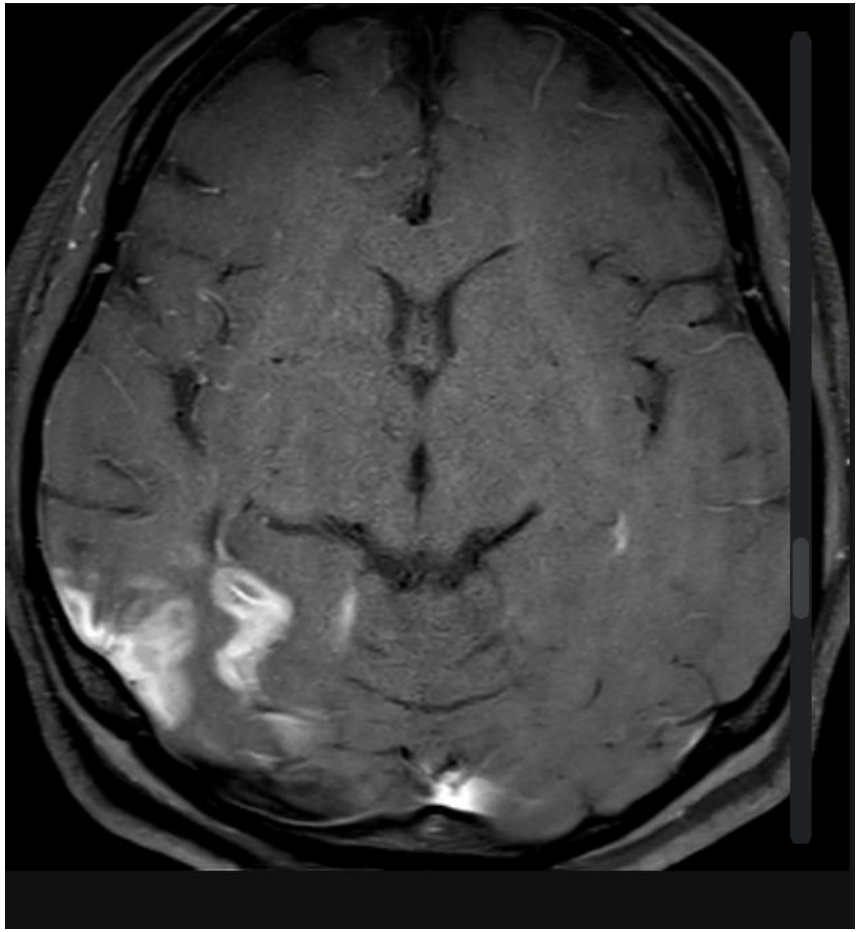
Nörosarkoidozis?

Behçet hastalığı ?

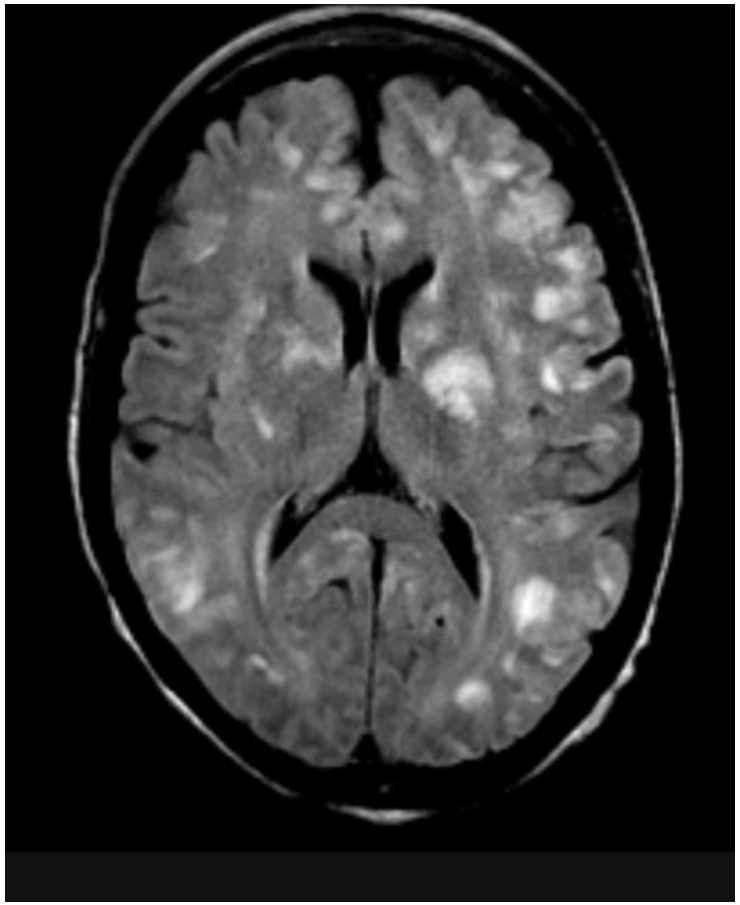
Vaskülit

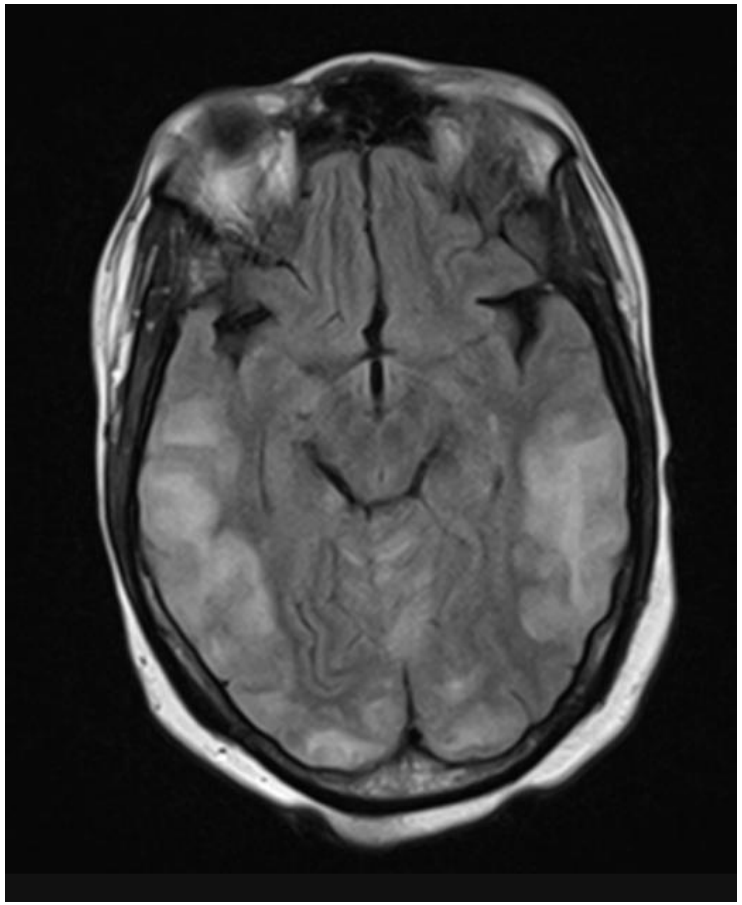


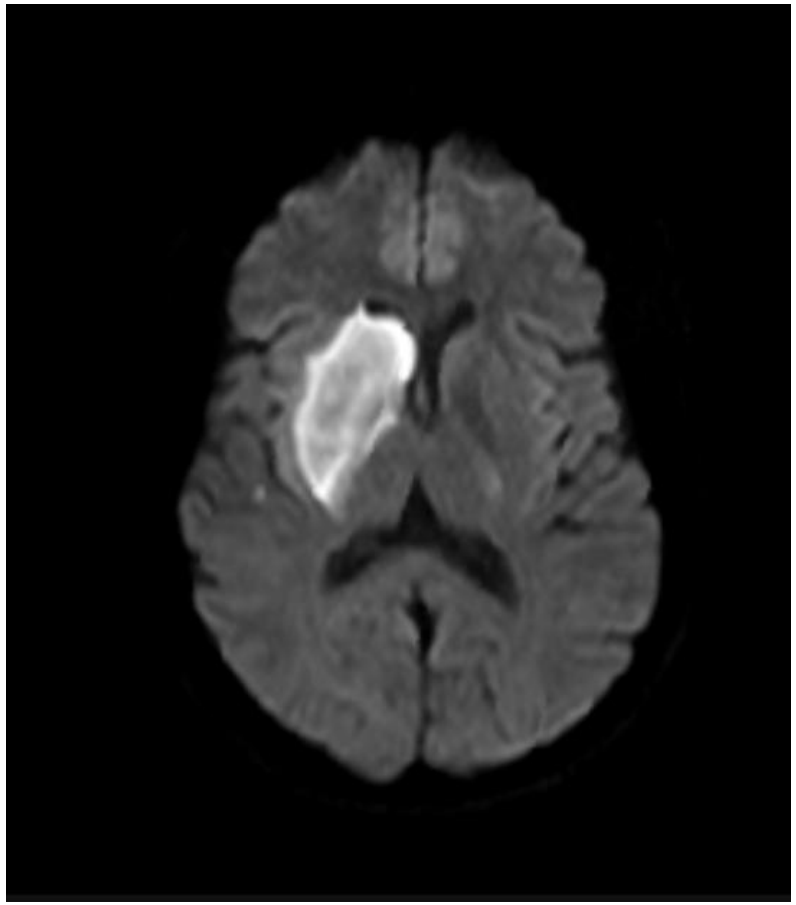




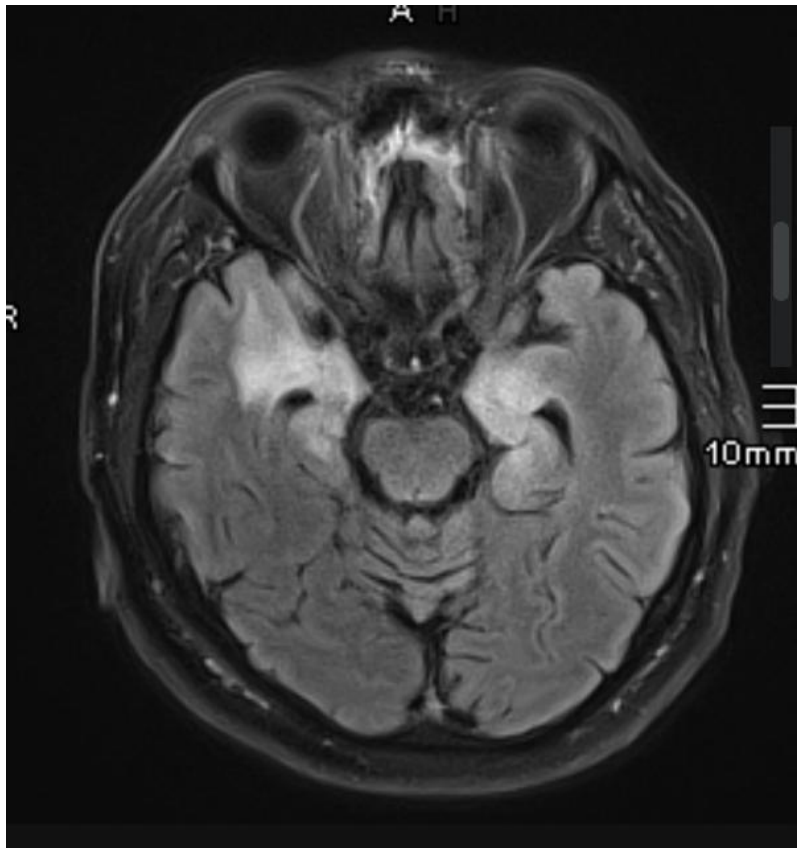
SLE

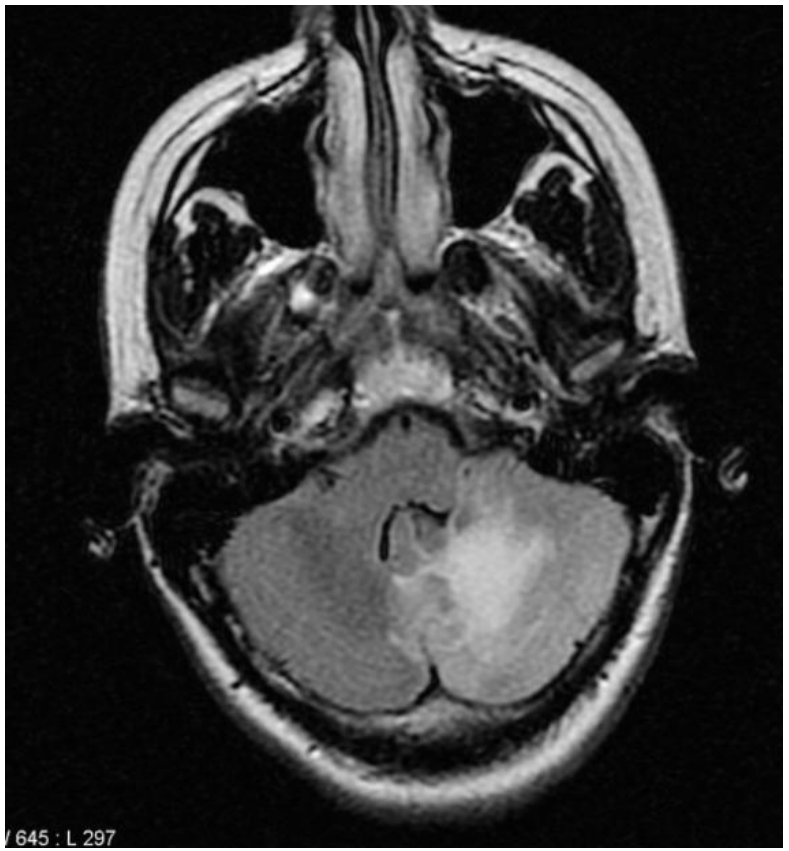


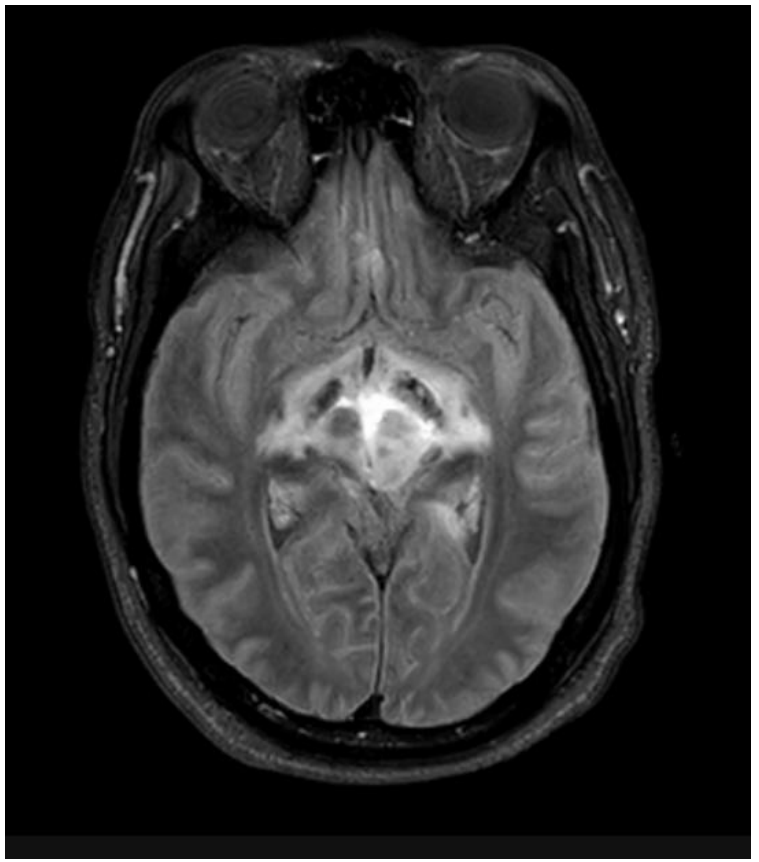




NÖROSARKOİDOZ







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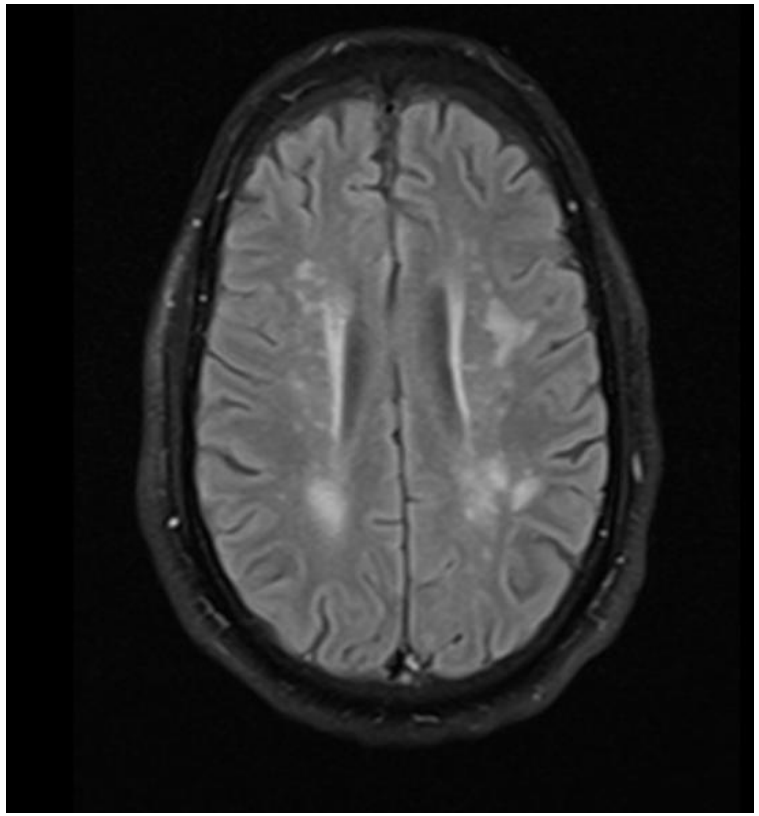
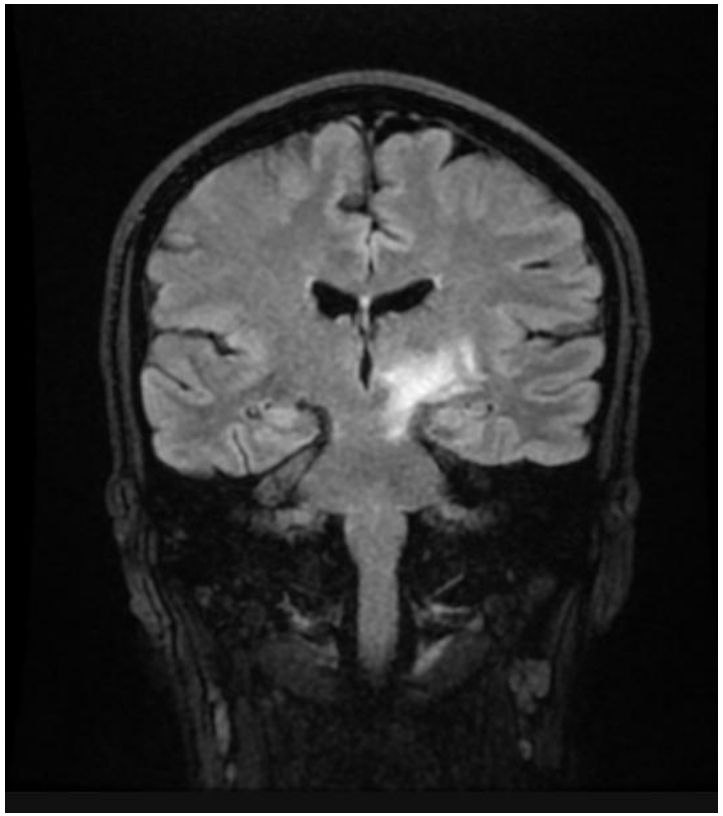
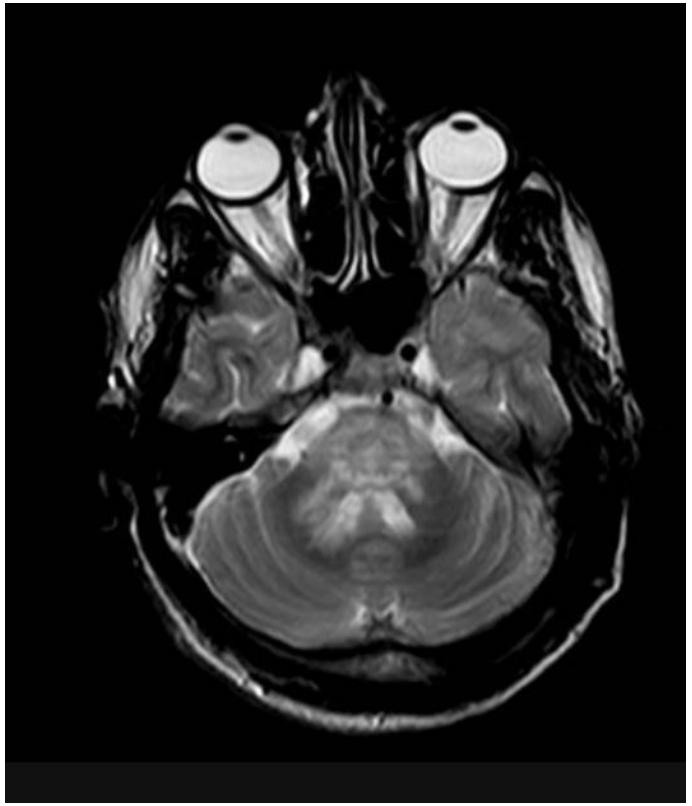






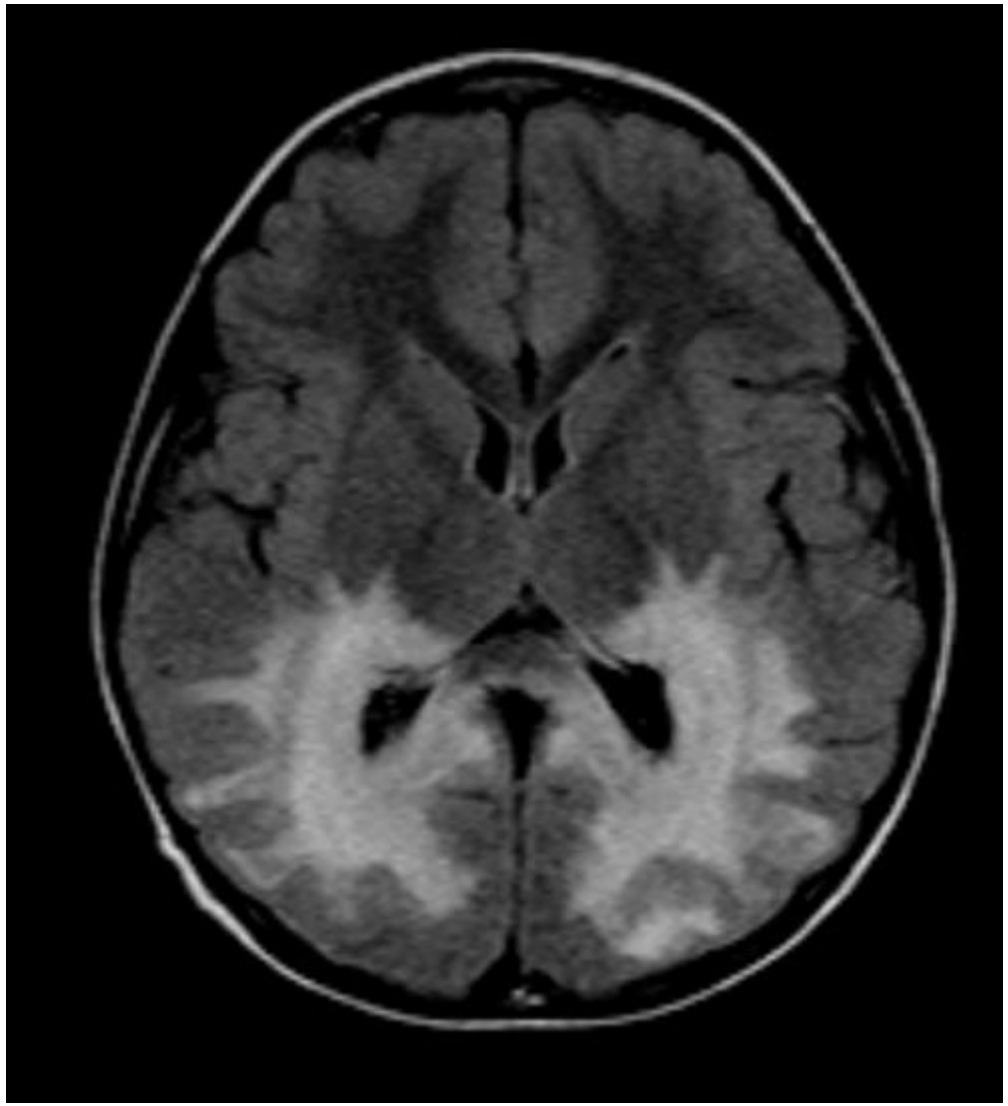
Metobolik ve nörodejeneratif hastalıkların nörolojik tutulumu?

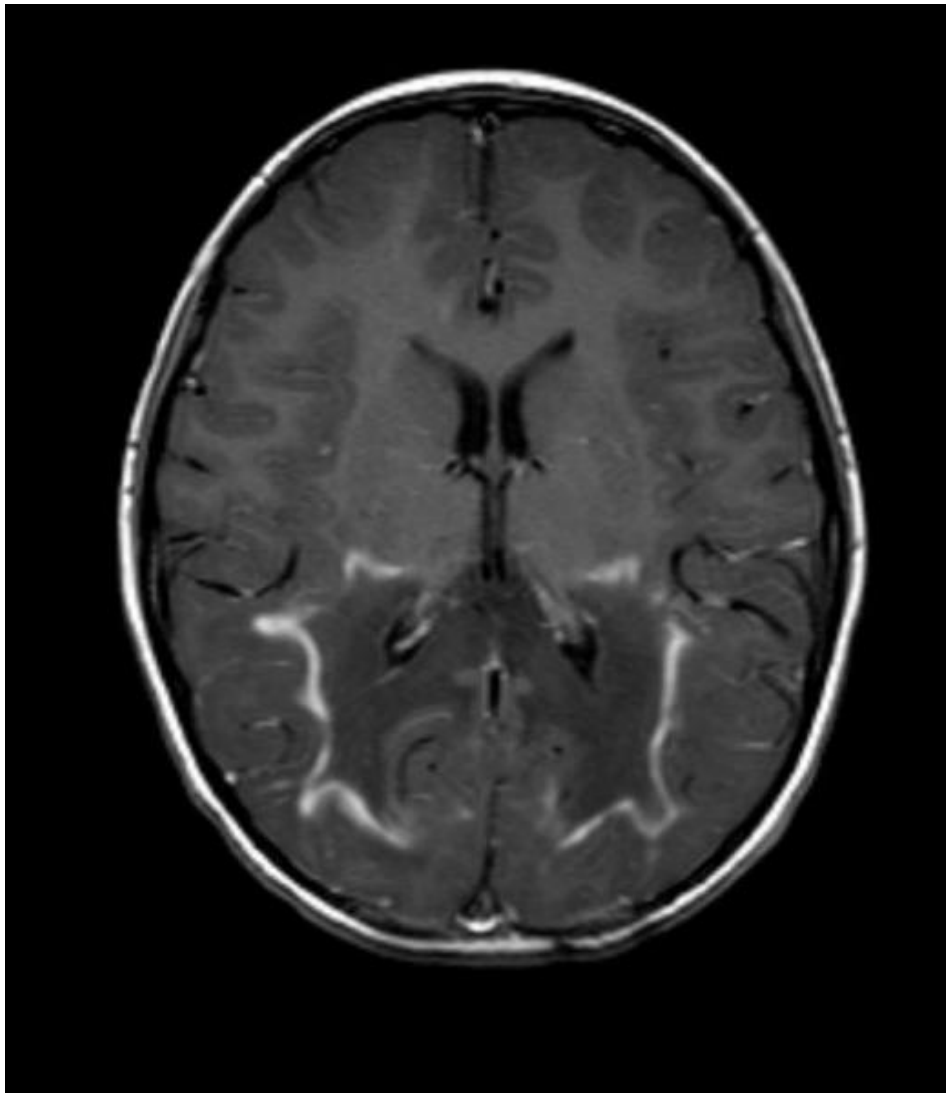
X geçişli adrenolökodistrofi ?

Mitokondriyal hastalıklar?

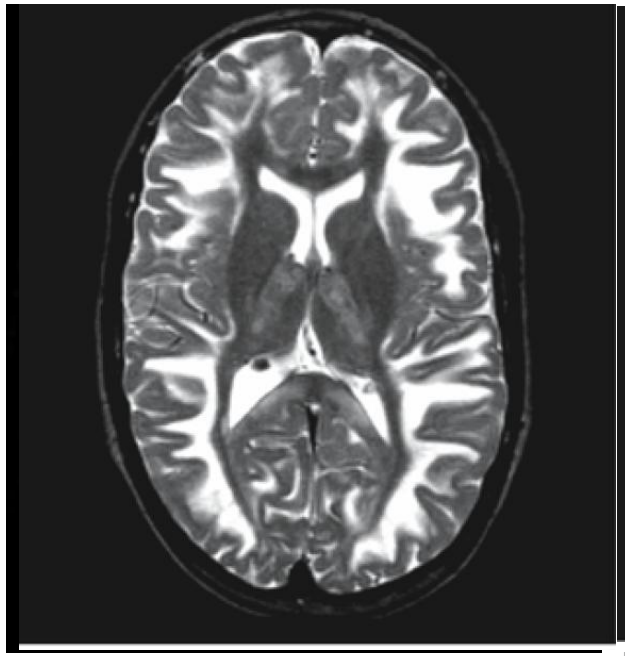
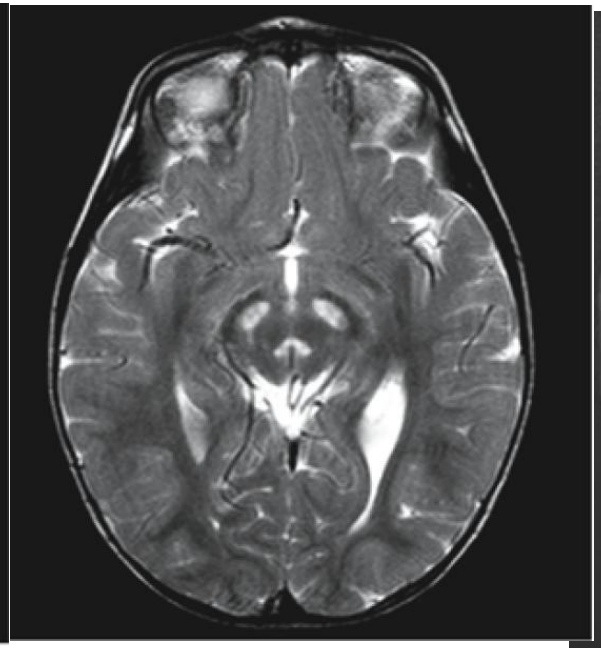
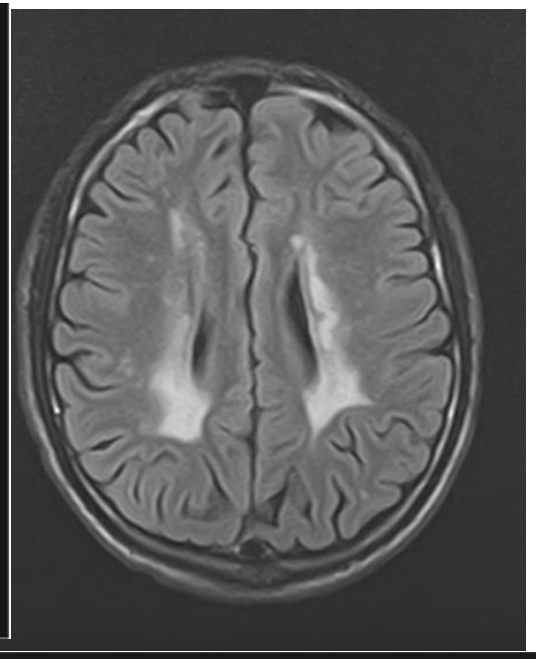
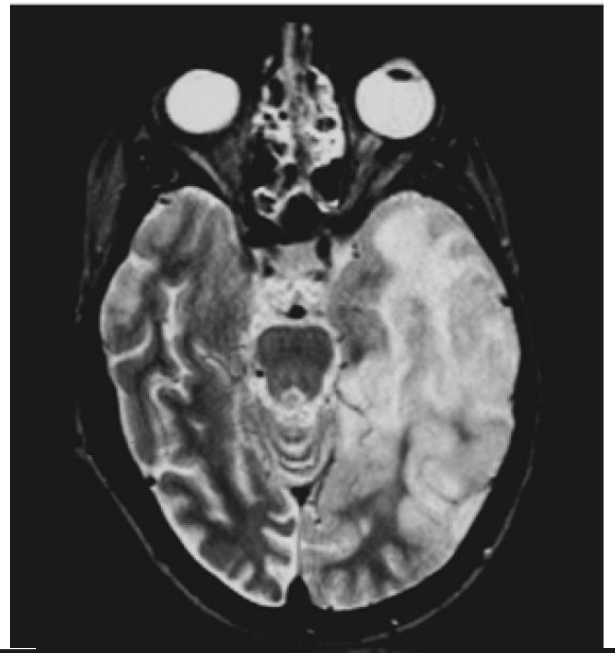
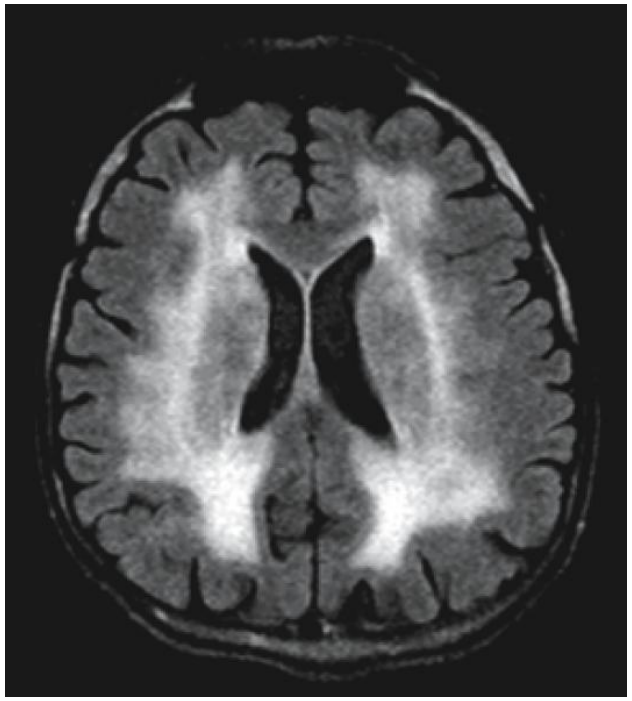
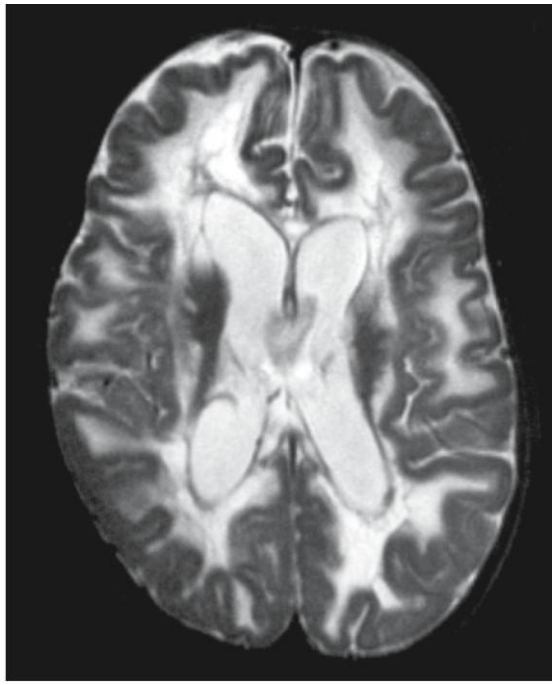
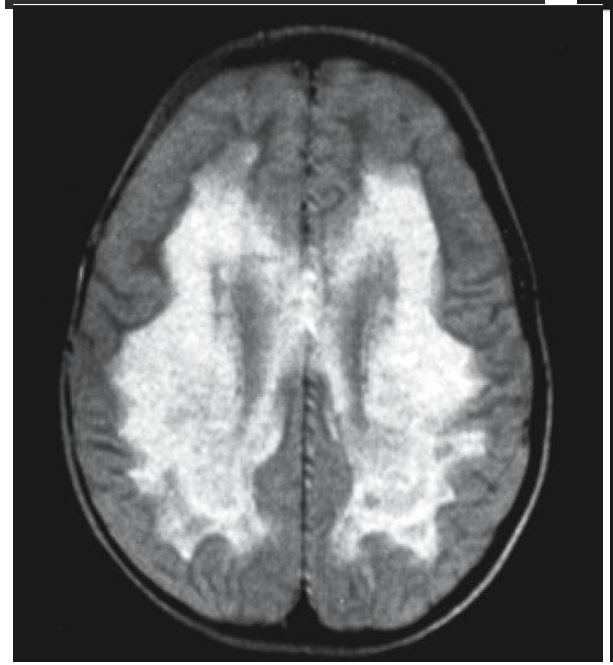
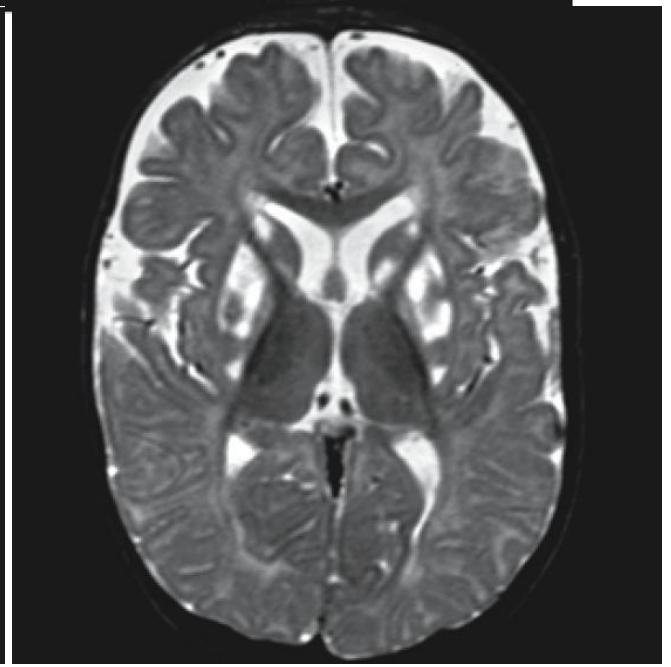
Aleksander hastalığı?

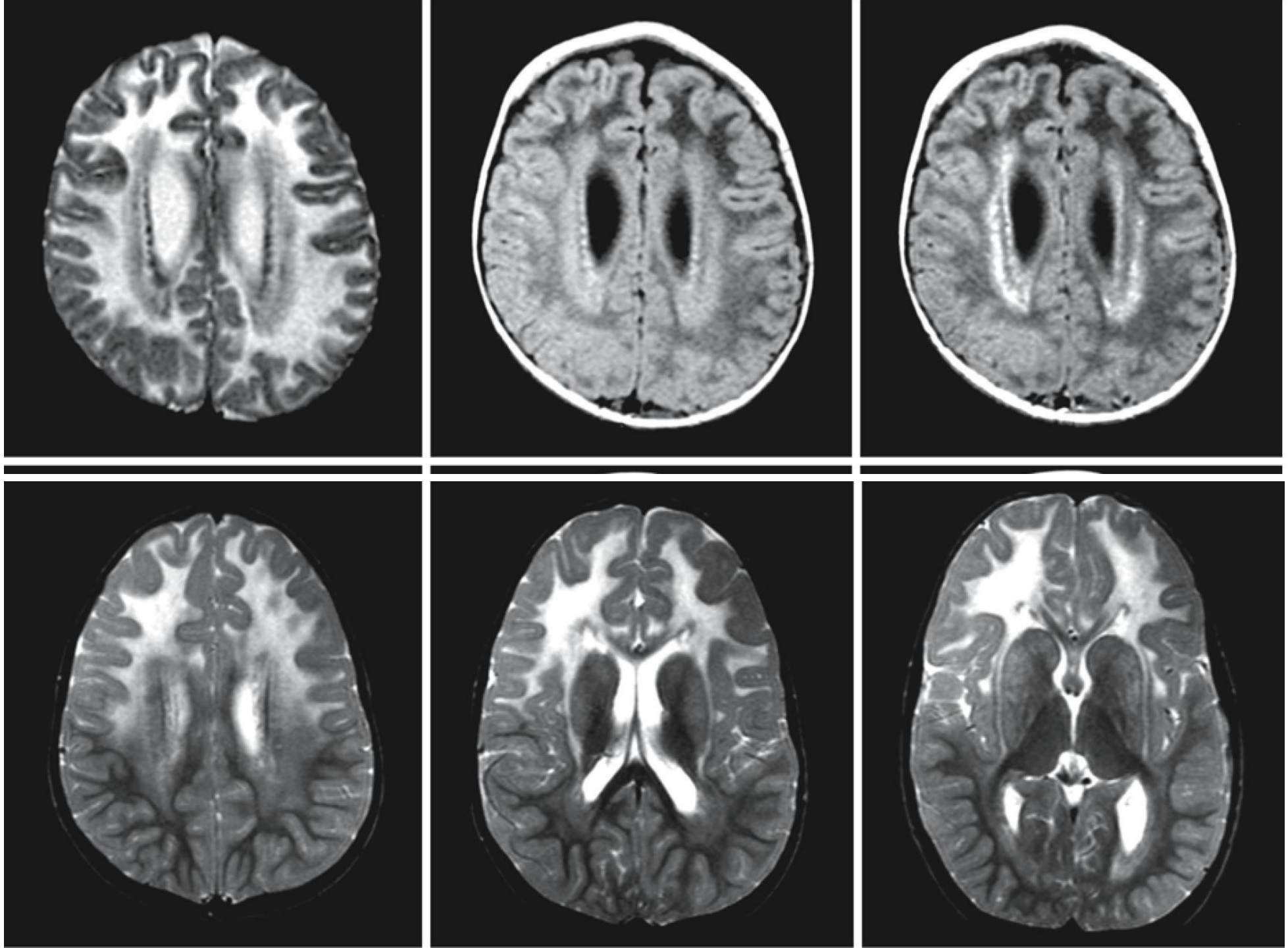
Adrenolökodistrofi



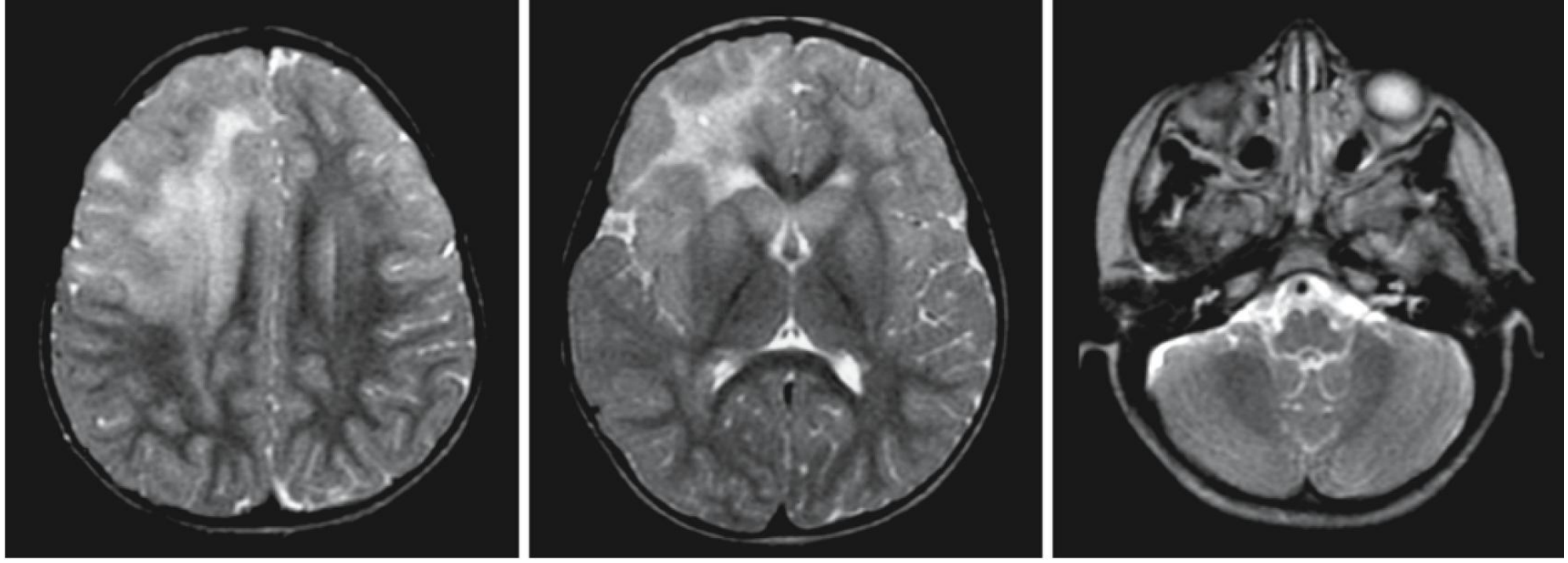


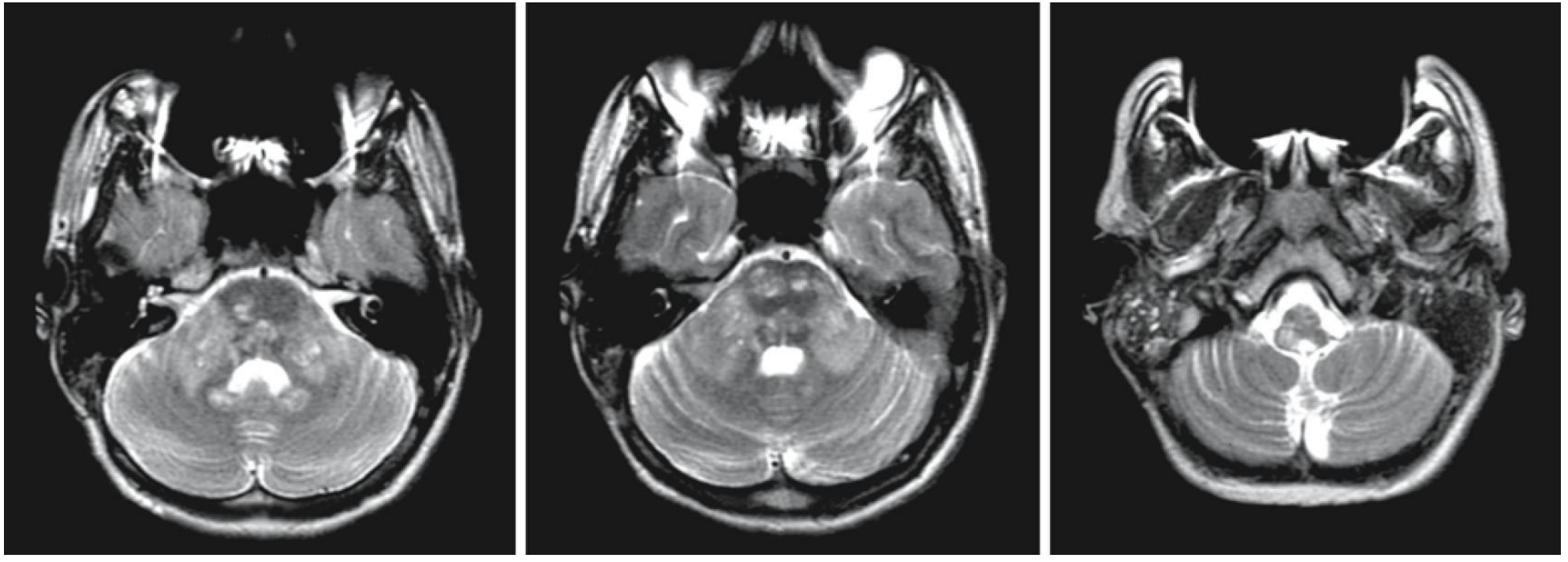
Mitokondriyal hastalıklar



Alexander hst





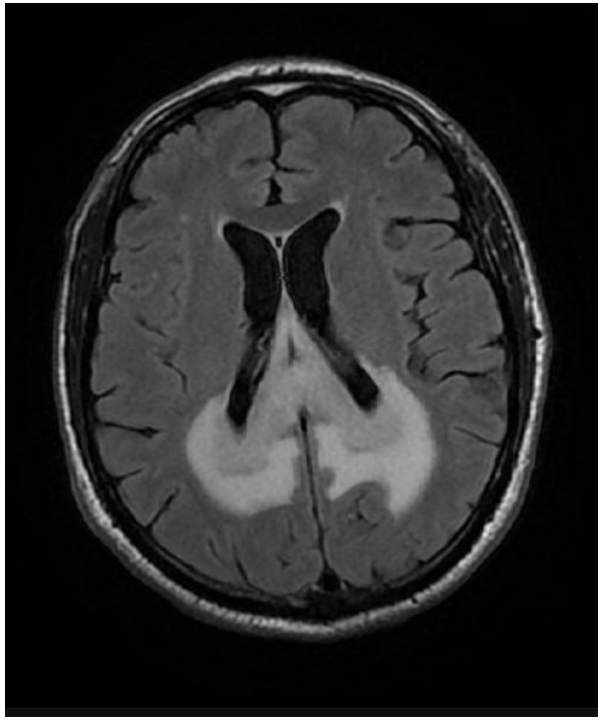
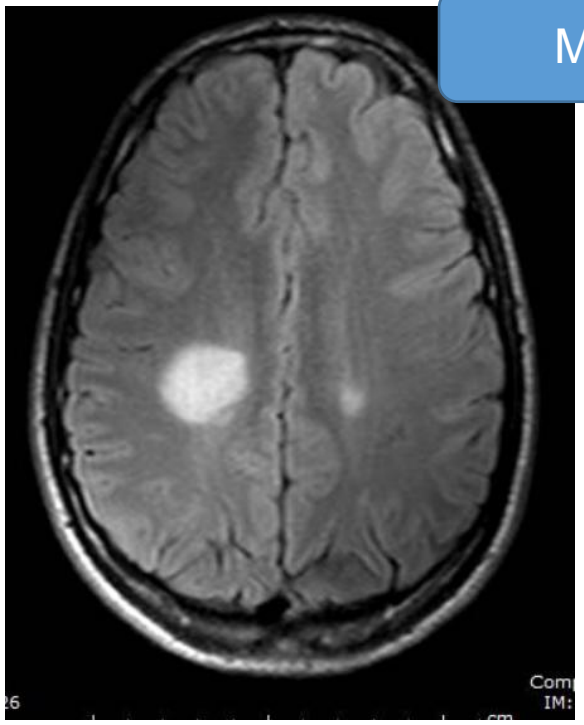
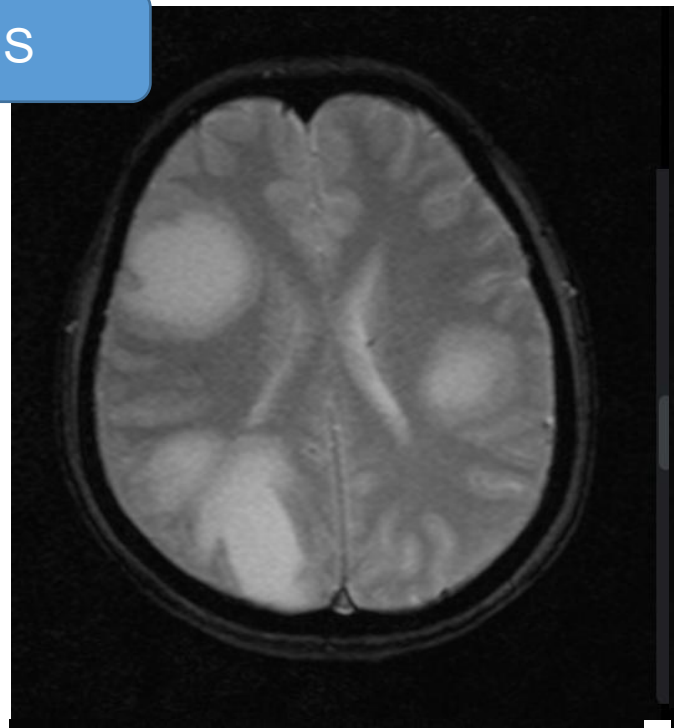
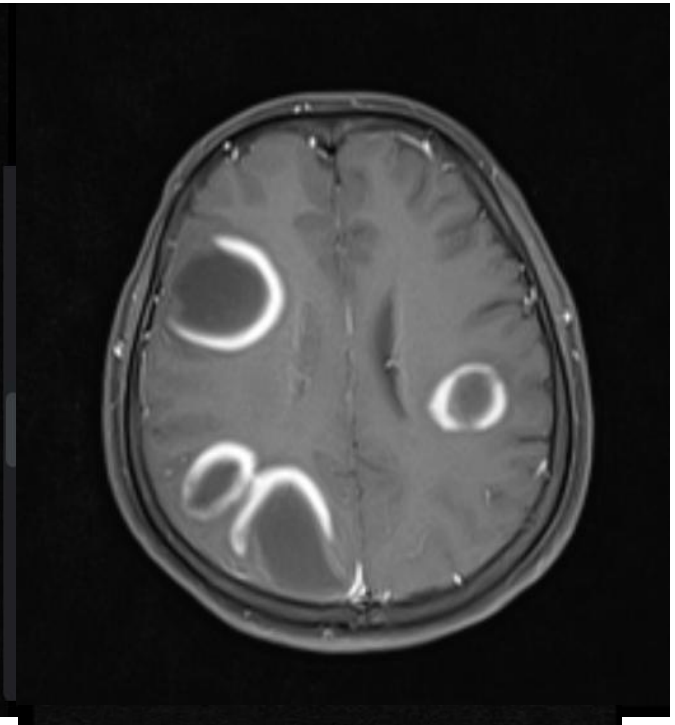
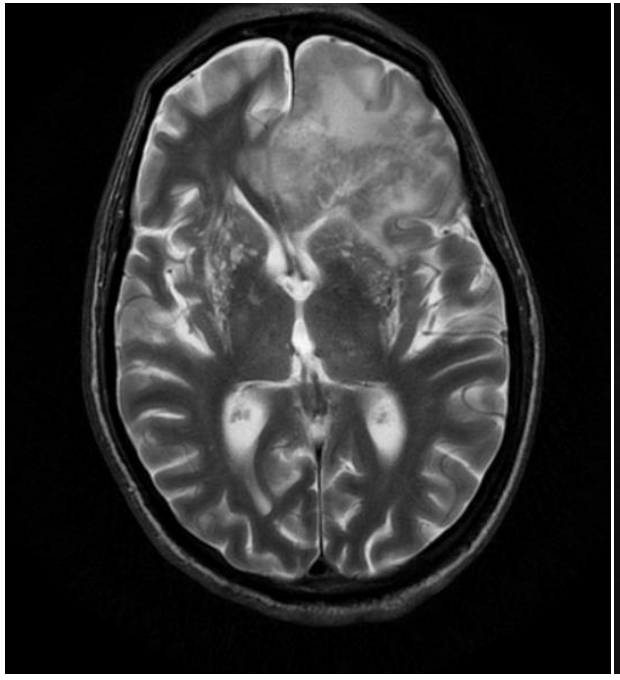
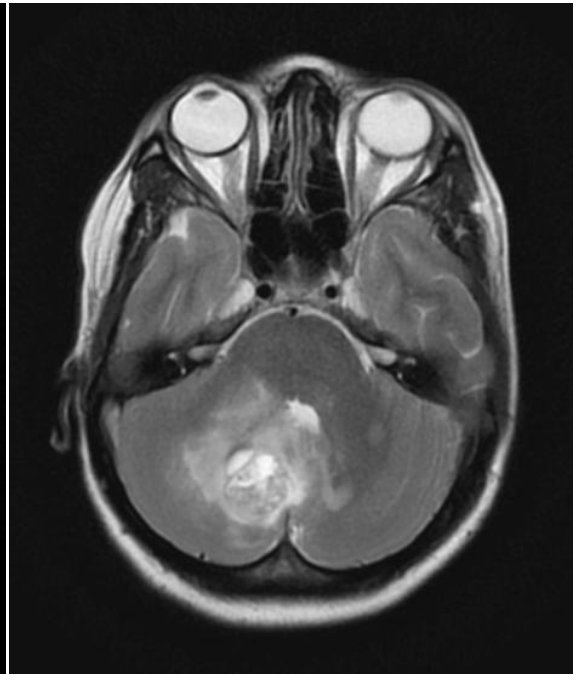
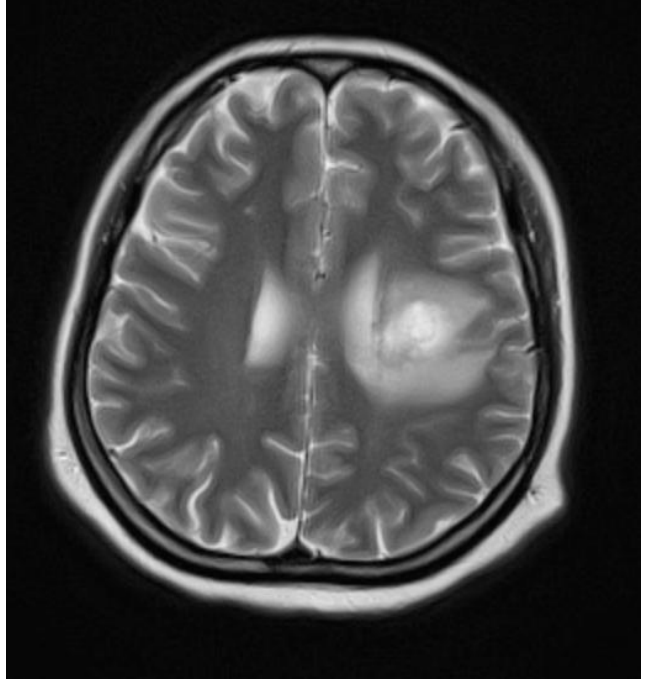
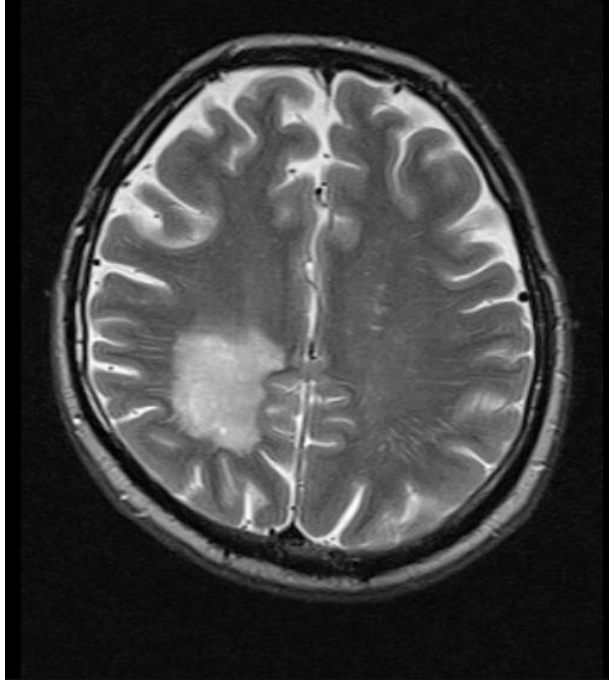
Atipik Alexander

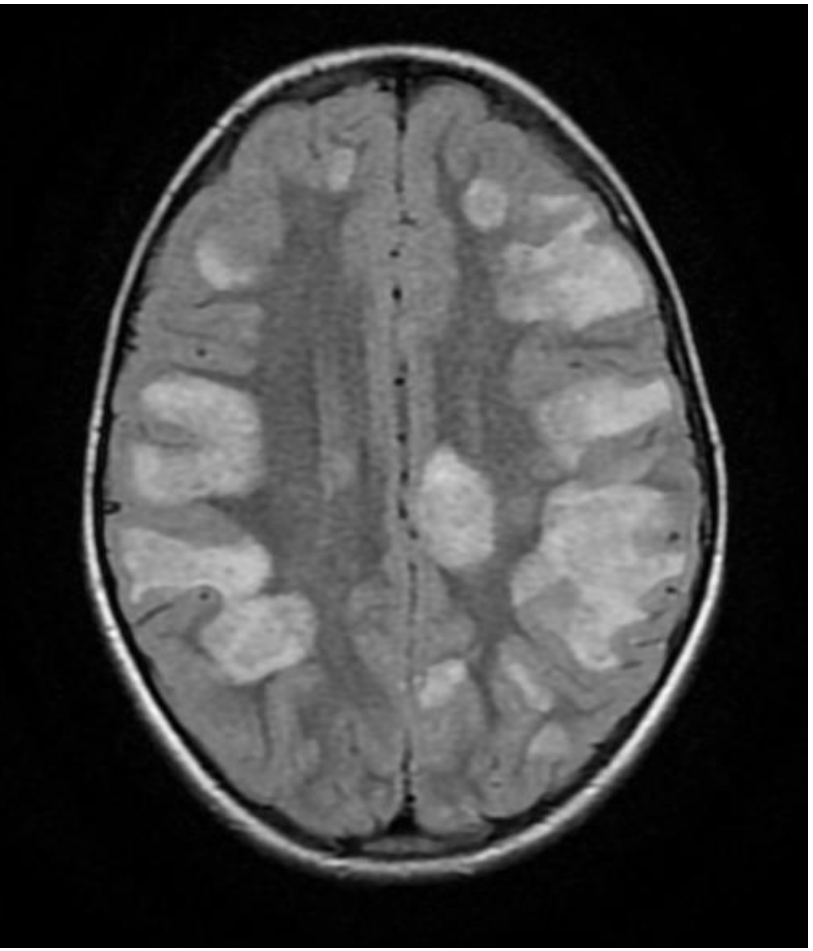
Demiyelinizan hastalıklar?

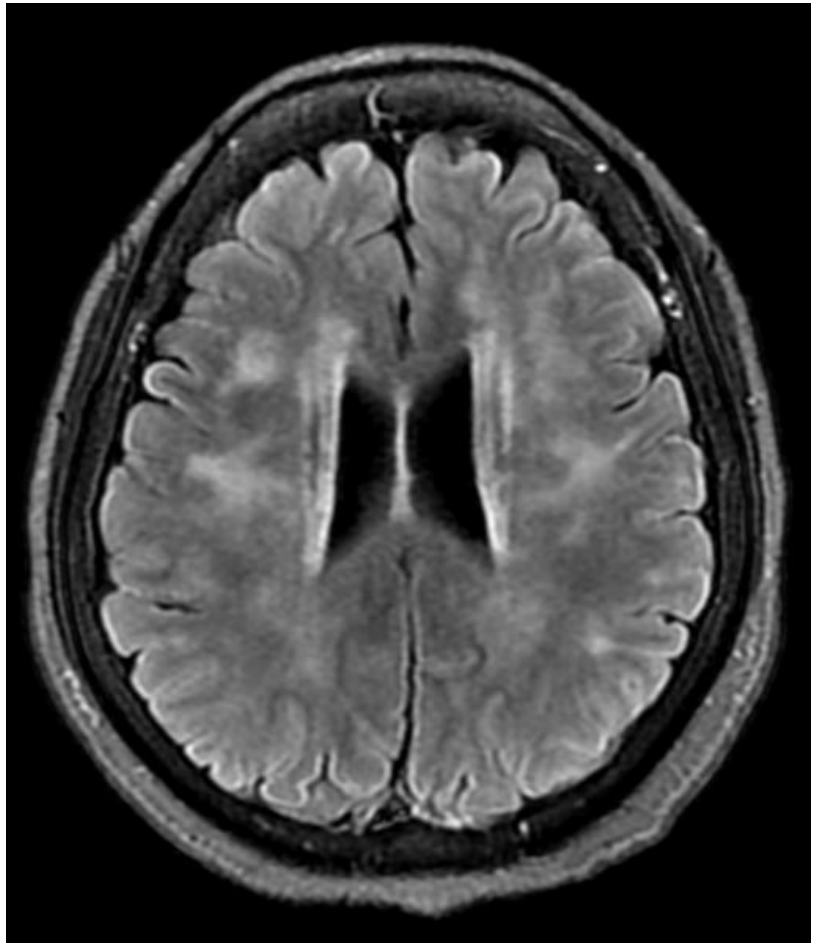
Multiple skleroz?

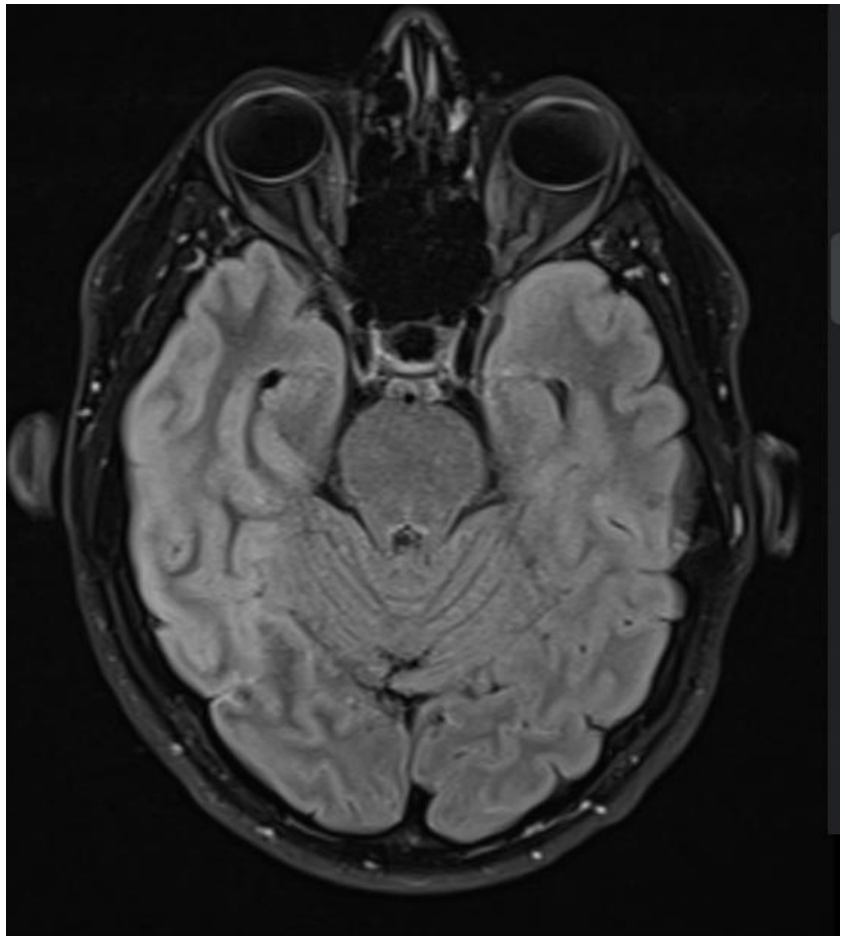
MOG ilişkili demiyelinizan hastalık?

MS







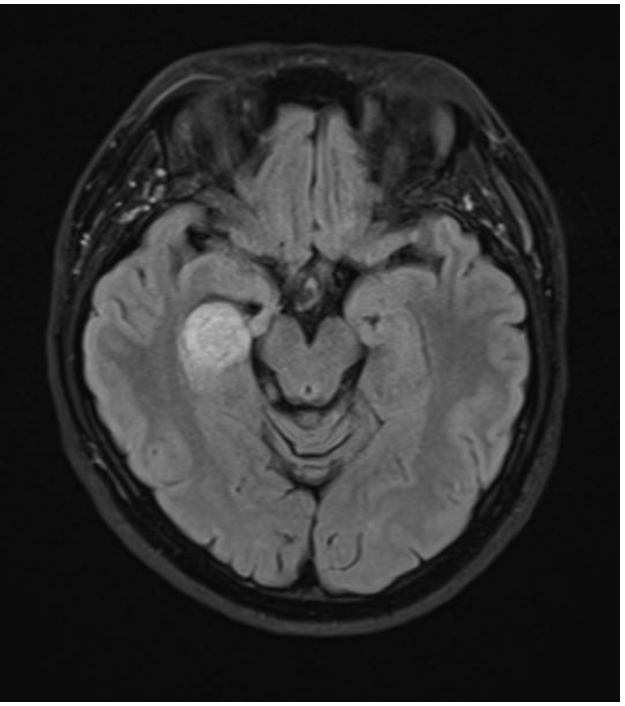
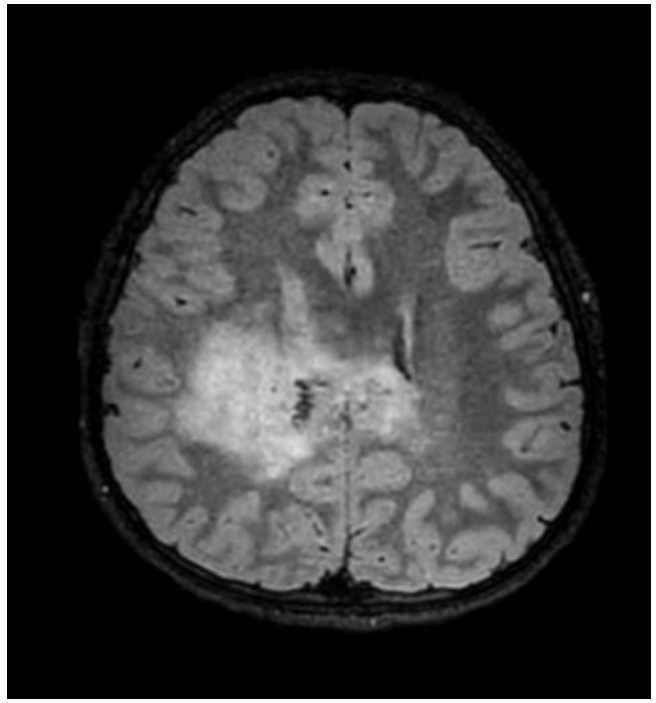
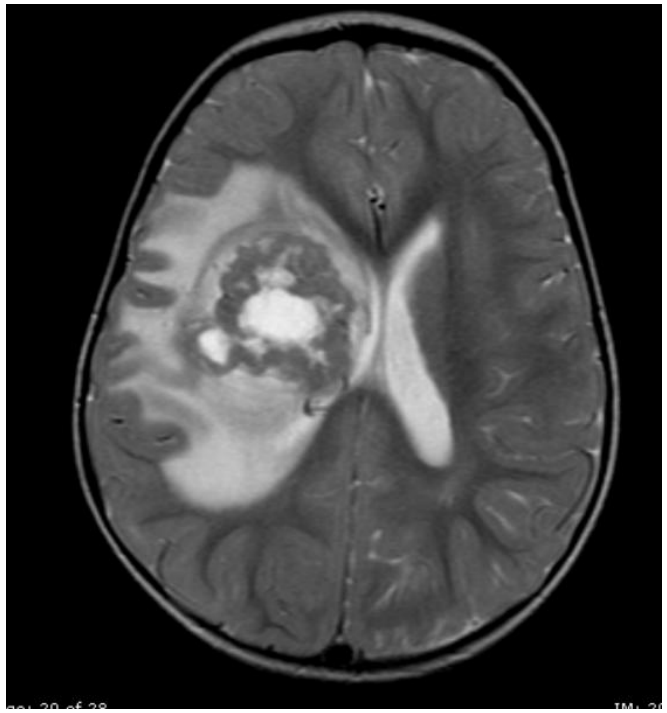
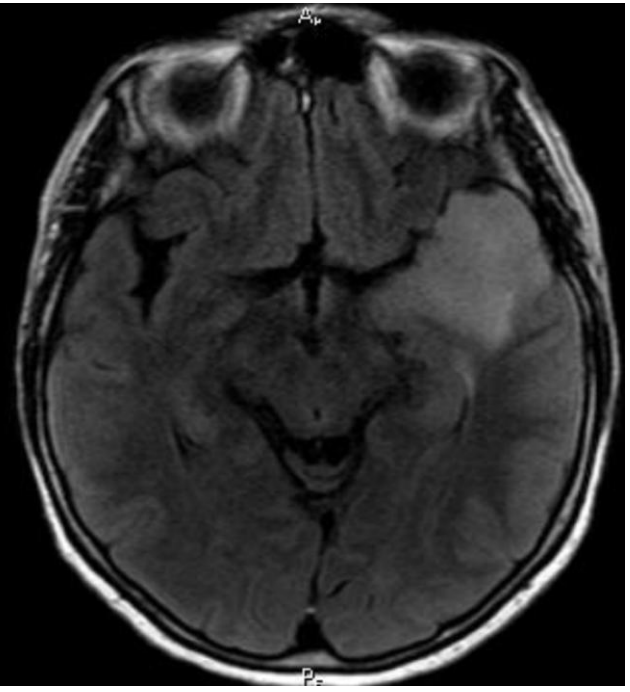
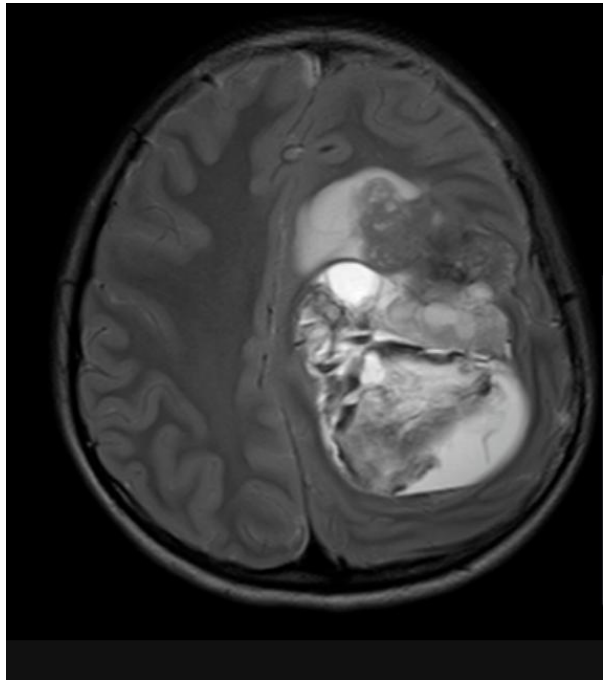
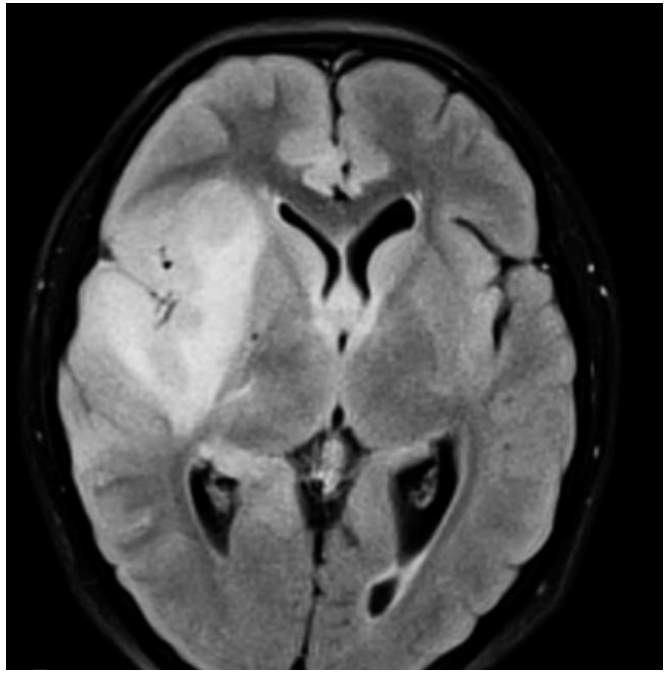
MOG ilişkili

SSS tümörleri?

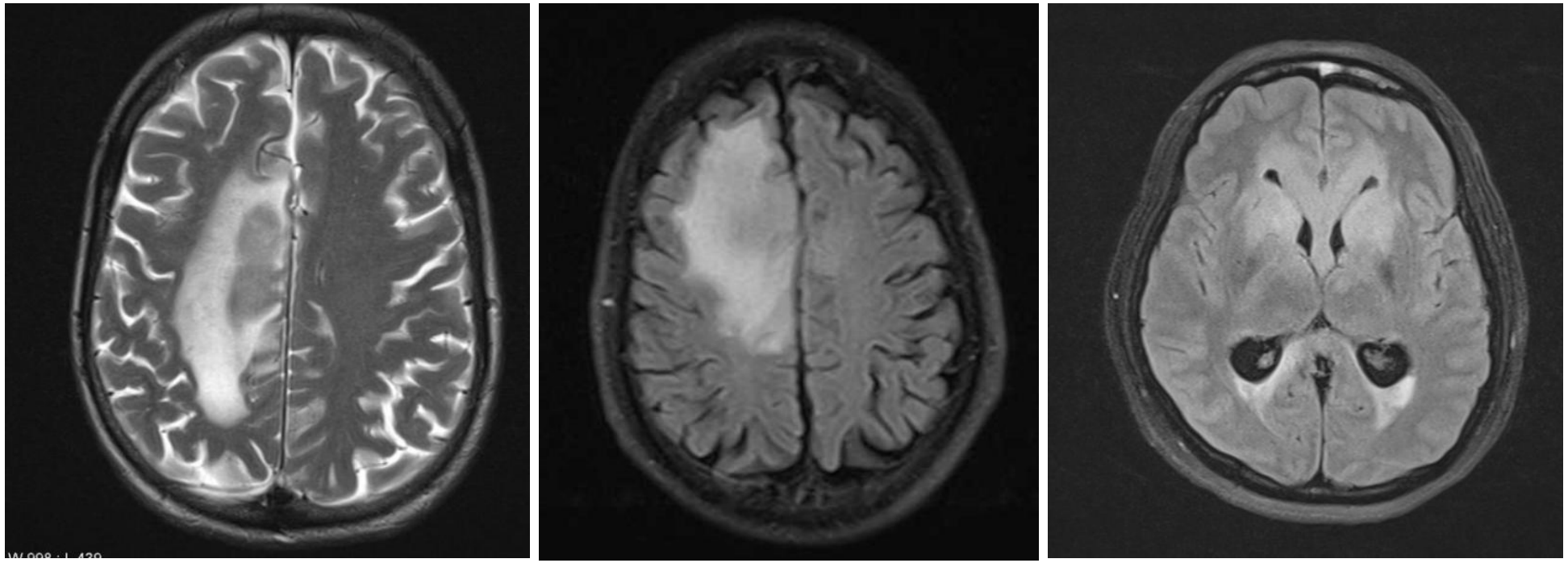
Primer?

Metastaz

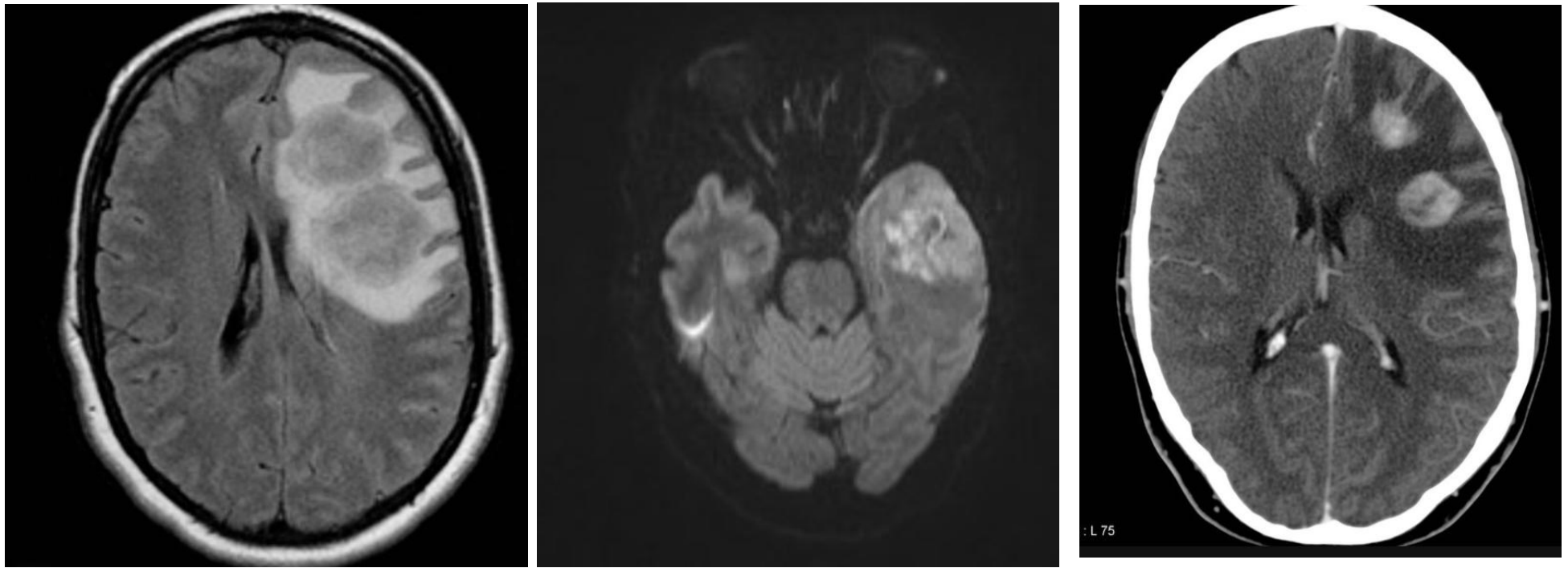
Lösemi, lenfoma?

SSS tümörleri



Lenfoma



Lösemi

Hangi tetkikler yapılabilir?

Görüntüleme?

Kan ve BOS tetkileri?

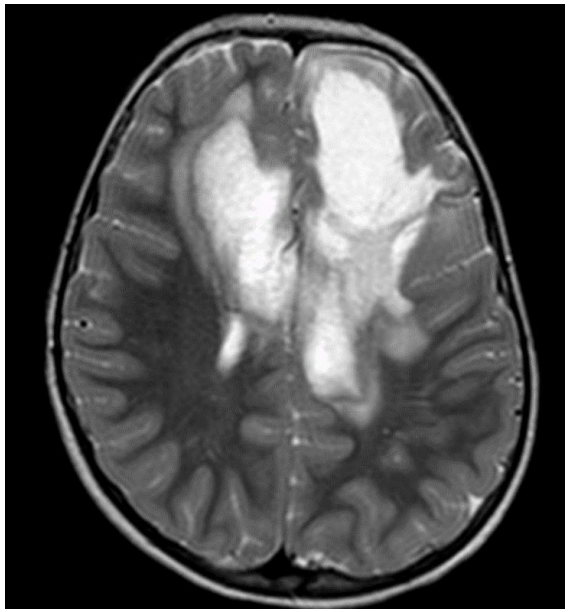
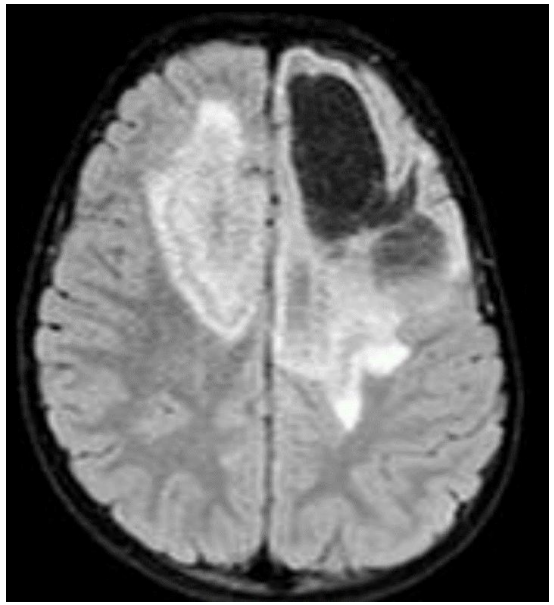
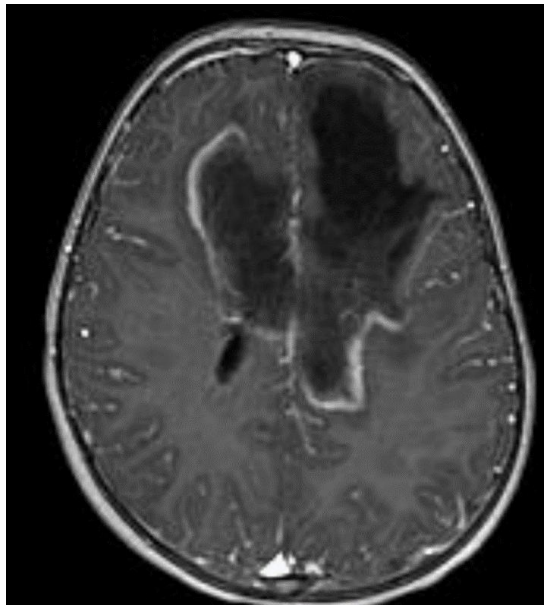
Doku örneklemesi?

Genetik testler?

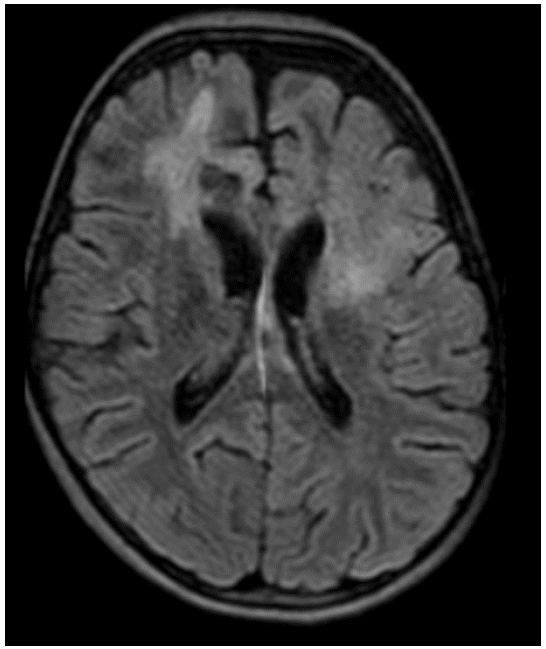
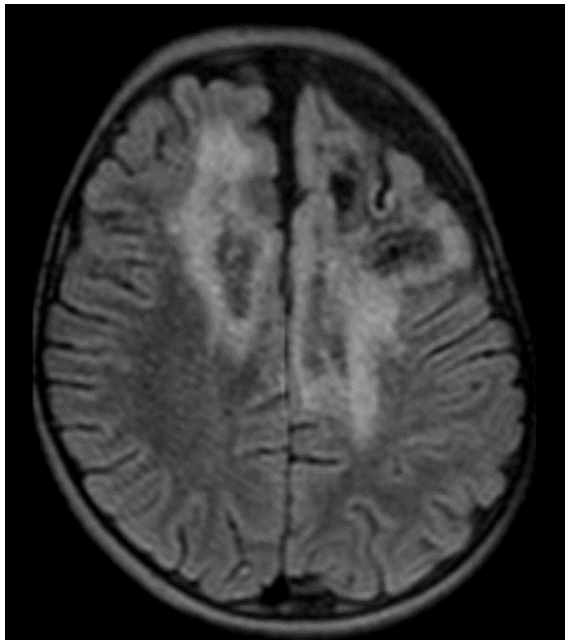
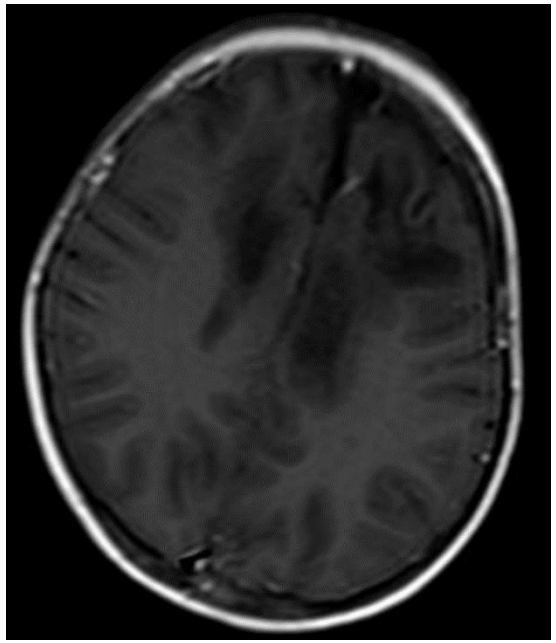
Görüntüleme

Mr spektroskopi: Cho/Cr oranında 2.38'e varan ve Cho/NAA oranında 2.44'e varan artışlar mevcuttur. Major lipit laktat pikleri mevcuttur. Ancak bu bulgular tümefaktif MS'de de görülebilir.

İlk planda demyelinizan/dismyelinizan süreçler düşünülmektedir. Ancak glial tümör ekarte edilemez.

5.6.2026

24.6.2026

Haziran 2025

BOS: İlk aşamada kontrendikasyon nedeniyle LP yapılamadı

Serum: MOG negatif

ANA, C3, C4 negatif, P-ANCA, C-ANCA ve diğer tüm Vaskülit ve otoimmün belirteçler: Negatif

Tüm Viral ve bakteriyel belirteçler: Negatif

Tüm metabolik hastalık testleri: Normal (2 kez)
İmmunoglobulinler, seruloplazmin, alfa 1 antitripsin, çölyak antikorları,
Sfingomyelinaz, hekzozaminidaz, Arilsülfataz A: normal
Galaktozilseramidaz (Lökosit): düşük

-Haziran 2025 patoloji:

Beyaz madde içinde yaygın mikroglia/makrofaj infiltrasyonu, damarlar çevresinde mikroglia/makrofaj ve lenfositelrden oluşan bant tarzı birikim, lümenleri makrofaj içeren küçük mikrokist formasyonları, beyaz maddede miyelin kaybı, kortekse görece korunmuş görünüm (lökodistrofi?)

Ağustos 2025

Lizozomal enzimler (Serum/Plazma)

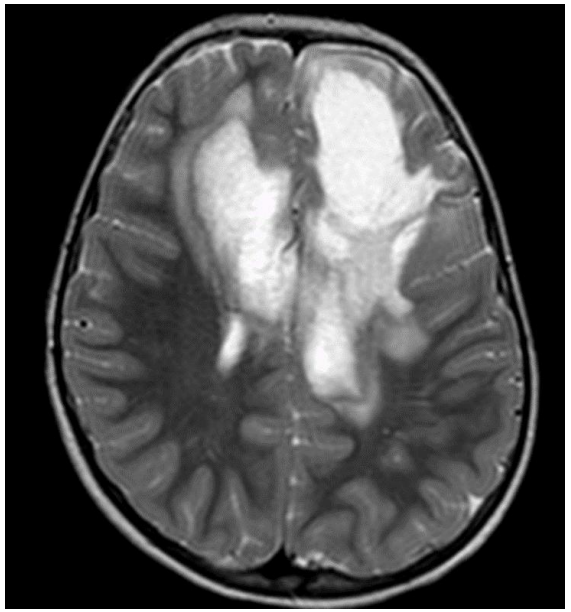
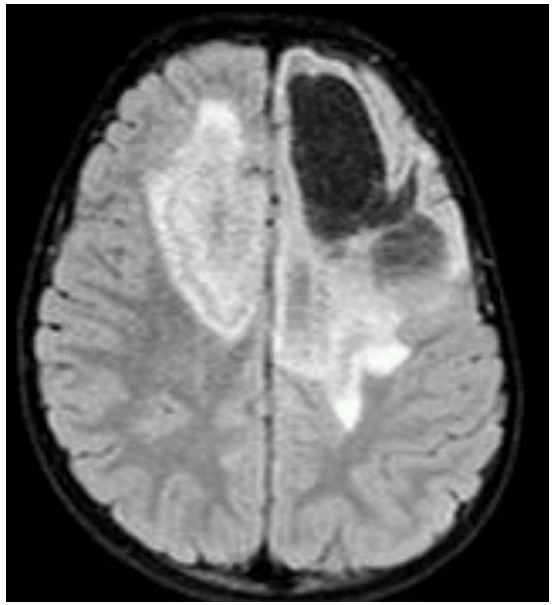
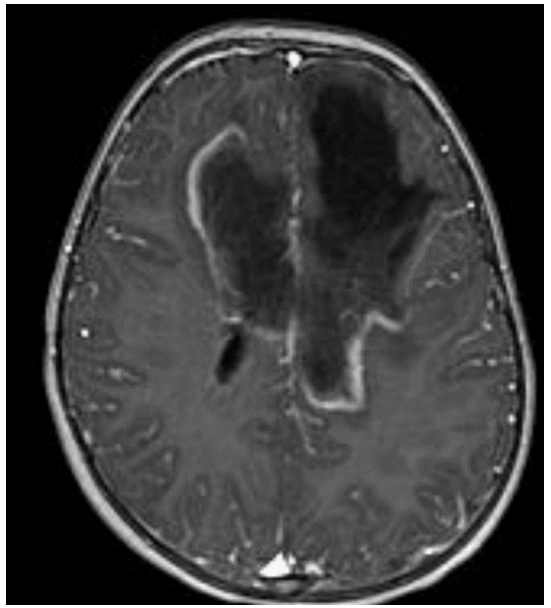
This action doesn't belong to me

Process Name : Lyso-GM1 ve Lyso-GM2, Serum	**Result :** sonuç ektedir	**Result Unit :**	**Reference Value :**
Process Name : Lyso-GM1 (Monosialoganglioside 1)	**Result :** <1	**Result Unit :** nmol/L	**Reference Value :** < 1,00
Process Name : Lyso-GM2 (Monosialoganglioside 2)	**Result :** <1	**Result Unit :** nmol/L	**Reference Value :** < 1,00
Process Name : Lyso-GM1-GM2 Yorum	**Result :** Lizosfingolipid (Lyso-GM1 ve Lyso-GM2) panelinde görülen değişimler non-spesifik olarak değerlendiri	**Result Unit :**	**Reference Value :**

Lizozomal enzimler (Serum/Plazma)

This action doesn't belong to me

Process Name : Lizospingolipid Paneli	**Result :** sonuç ektedir	**Result Unit :**	**Reference Value :**
Process Name : Lyso-Gb1 (Glucosylsphingosine)	**Result :** 0,40	**Result Unit :** nmol/L	**Reference Value :** < 3,70
Process Name : Lyso-Gb3 (Globotriaosylceramide)	**Result :** 0,30	**Result Unit :** nmol/L	**Reference Value :** < 0,90
Process Name : Lyso-SM (Sphingomyelin)	**Result :** 1,20	**Result Unit :** nmol/L	**Reference Value :** < 3,40
Process Name : Lyso-SM509 (N-pal.-O-phos., PPCS)	**Result :** 21,70	**Result Unit :** nmol/L	**Reference Value :** 1,00 - 33,00

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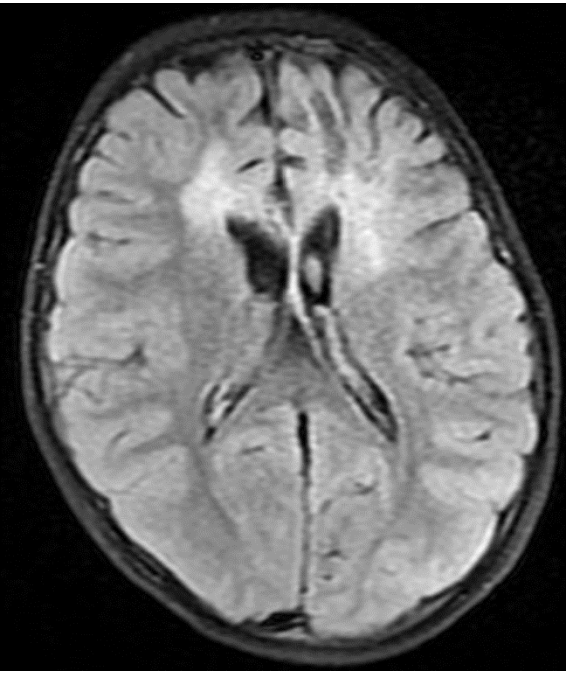
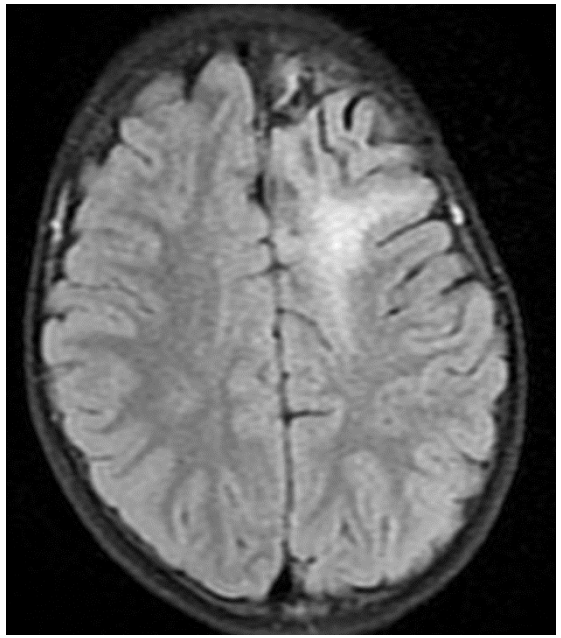
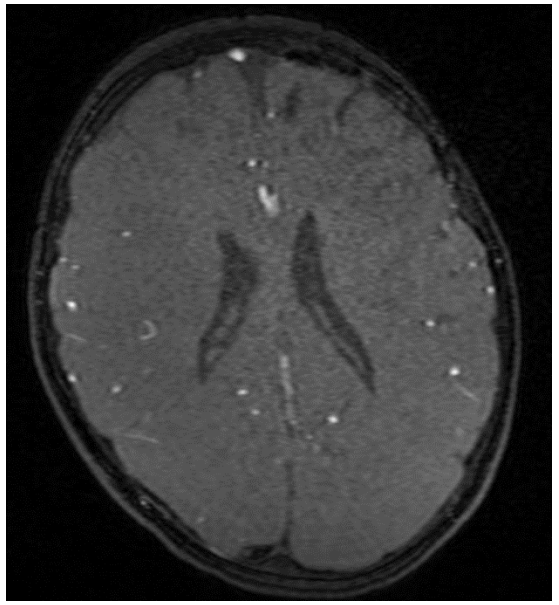
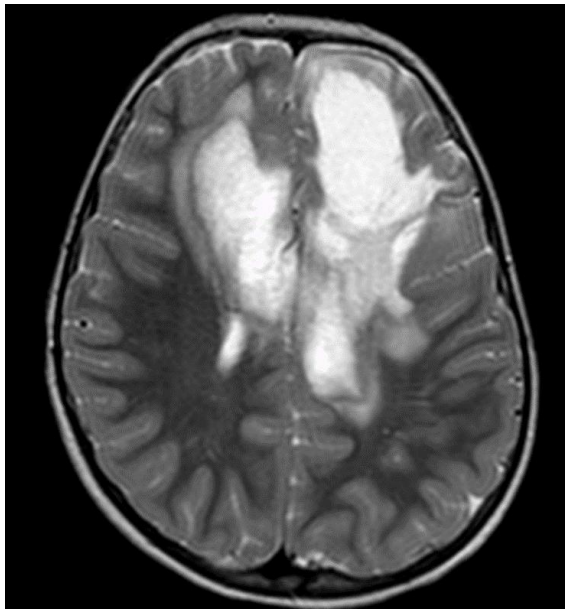
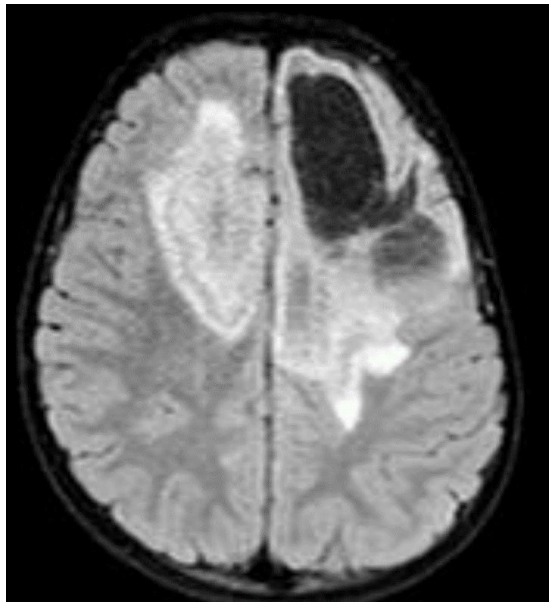
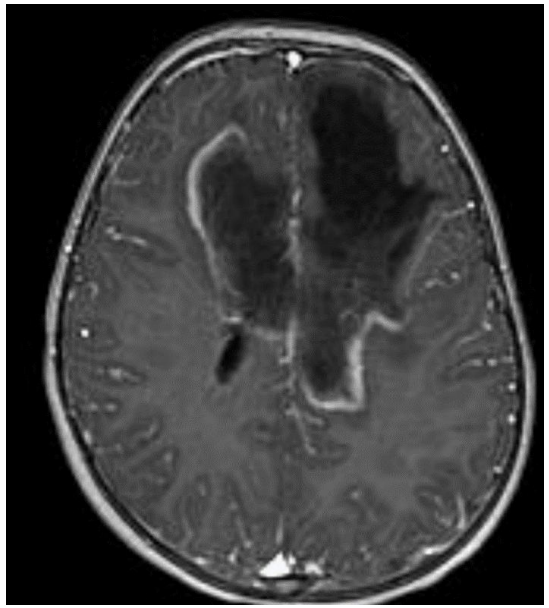




17.10.2025

MUAYENE TARİHİ: 18/11/2025

Genel durumu iyi, bilinç açık, koopere oryante
Pupiller izokorik dır /ıdır:++/++
Göz hareketleri sol göz üste bakış kısıtlı+,
Nistagmus yok
Fasikülasyon yok
Göz dibi: normal.
Pitosis yok
Fasiyal asimetri yok
Diğer kraniyal sinirler intakt
Kas gücü doğal
Tonus doğal
Dtr ler normoaktif klonus yok
Serebellar testler becerikli
Yürüyüş paterni olağan

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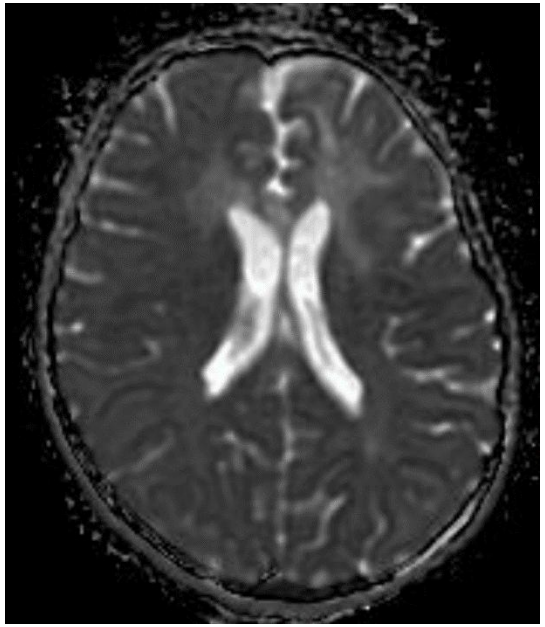
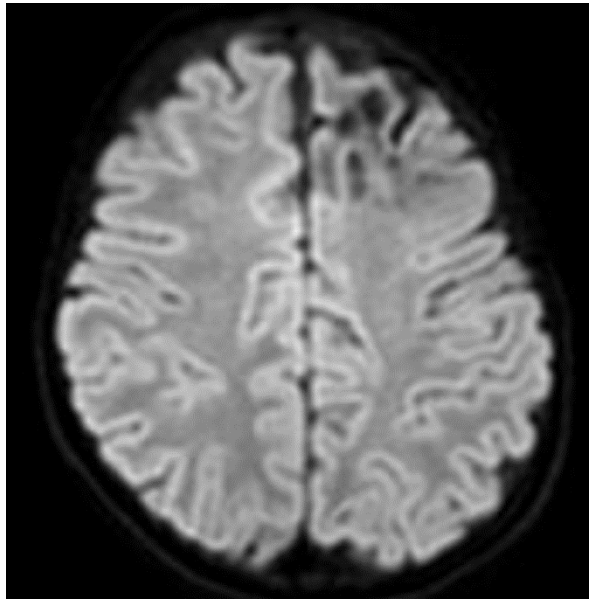



8.01.2026

Eylül 2025

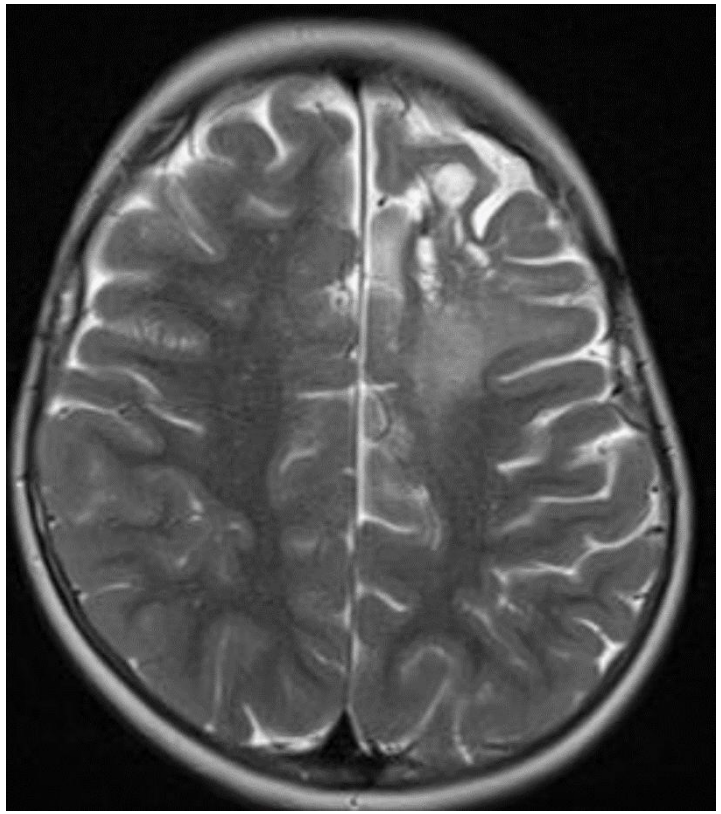
Tekrar viral markerlar, otoimmün markerlar : negatif

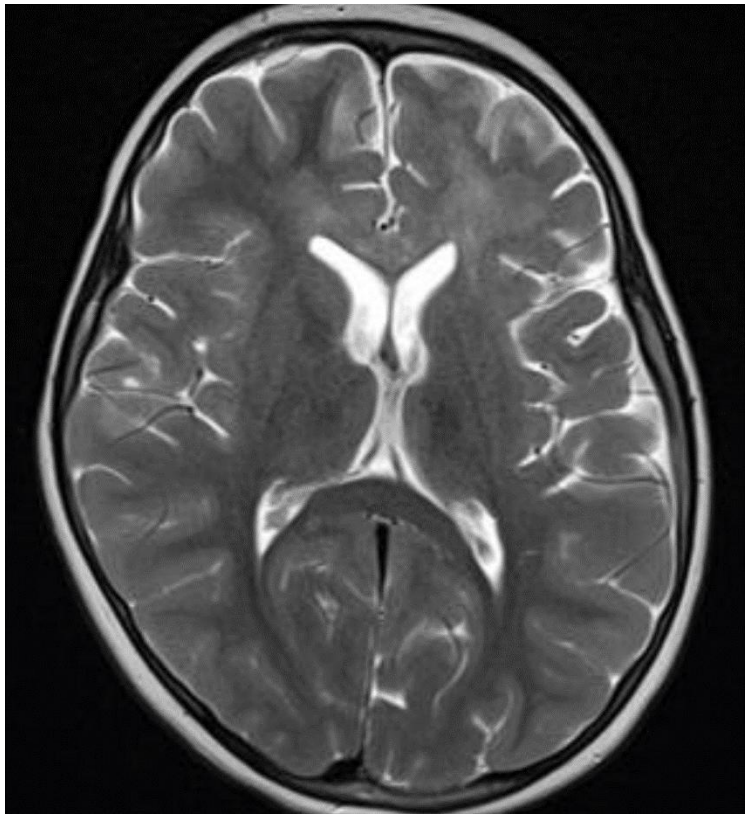
2 kez BOS oligoklonal band ve diğer demiyelinizan marker: Negatif

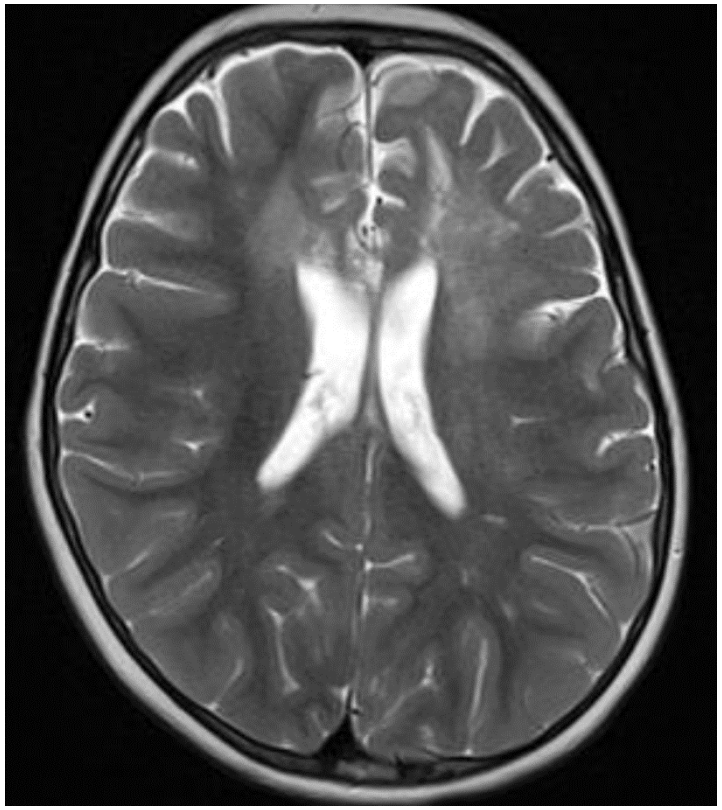
Ocak 2026: tekrar immün yetmezlik testleri: Normal

Tekrar metabolik testler ve lizozomal enzim tekrarı: normal

Şubat 2026







WGS

* 608302

LEUCINE-RICH GENE, GLIOMA-INACTIVATED, 3; LGI3

HGNC Approved Gene Symbol: LGI3

Cytogenetic location: 8p21.3 Genomic coordinates (GRCh38) : 8:22,146,830-22,156,806 (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
8p21.3	Intellectual developmental disorder with muscle tone abnormalities and distal skeletal defects	620007	AR	3

INHERITANCE
- Autosomal recessive

HEAD & NECK

Face
- Facial myokymia

Eyes
- Periorbital movements

Mouth
- Oromotor movements
- Small mouth
- Restricted mouth movements
- Tongue fasciculations

CHEST

Diaphragm
- Diaphragmatic hernia (in some patients)

ABDOMEN

External Features
- Umbilical hernia (in some patients)

SKELETAL

Pelvis
- Hip contractures
- Hip dysplasia

Limbs
- Limb joint contractures

Hands
- Tapering fingers
- Contracted fingers
- Fisted hands

Feet
- Foot deformities

MUSCLE, SOFT TISSUES
- Hypotonia
- Hypertonia
- Facial myokymia
- Distal muscle atrophy (in some patients)
- Near continuous movements seen on EMG
- Fasciculations
- Fibrillations

NEUROLOGIC

Central Nervous System
- Global developmental delay
- Impaired intellectual development, mild to moderate
- Speech delay
- Learning difficulties
- Delayed walking by a few years
- Unsteady gait
- Seizures (rare)

Peripheral Nervous System
- Hyporeflexia
- Areflexia

Behavioral Psychiatric Manifestations
- Autism spectrum disorder (in some patients)
- ADHD (in some patients)

MISCELLANEOUS
- Onset in early infancy

MOLECULAR BASIS
- Caused by mutation in the leucine-rich gene, glioma-inactivated, 3 (LGI3, 608302.0001)

▲ Close

619864

LEUKODYSTROPHY, CHILDHOOD-ONSET, REMITTING; CORLK

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
9q22.32	?Leukodystrophy, childhood-onset, remitting	619864	AD	3	FBP2	603027

INHERITANCE

- Autosomal dominant

ABDOMEN

Gastrointestinal

- Tube feeding (during the acute episode)

NEUROLOGIC

Central Nervous System

- Normal early development
- Acute loss of developmental milestones (in late infancy)
- Irritability (during the episode)
- Loss of ability to sit or stand (during the episode)
- Poor motor activity
- Neurologic recovery
- Regaining of developmental skills
- Speech delay
- Persistent gait abnormalities
- Seizures (in some patients)
- Leukodystrophy on brain imaging, acute
- Leukodystrophy affects various brain regions
- Demyelination
- Resolution of white matter lesions over several months or years
- Remyelination over the following months and years
- Residual gliotic lesions on brain imaging

Behavioral Psychiatric Manifestations

- Psychiatric manifestations (in some patients)
- Psychosis
- Anorexia nervosa
- Drug addiction
- Schizophrenia

LABORATORY ABNORMALITIES

- Mitochondrial abnormalities in fibroblasts

MISCELLANEOUS

- Acute onset in the first year of life (some patients)
- Acute decompensation with loss of developmental skills is triggered by fever or infection
- Patients regain developmental skills over the following months and years
- Clinical improvement correlates with resolution of white matter abnormalities
- Variable phenotype
- One family has been reported (last curated May 2022)

BABADA aynı gen heterozigot

Annede normal

Kardeşler normal

Tekrar sorgulandığında babada benzer yaşlarda benzer bir durum yaşadığını, dönemin şartlarında hastaneye götürülmediğini ve babanın karar alma süreçlerinde zorluk yaşadığını ve babanın kardeşlerinin bazılarında benzer durum olduğu öğrenildi. ?

doi:10.1093/braincomms/fcab036 BRAIN COMMUNICATIONS 2021: Page 1 of 15 | 1

BRAIN COMMUNICATIONS

A novel remitting leukodystrophy associated with a variant in *FBP2*

Agnieszka Gizak,[1,†] Susann Diegmann,[2,†] Steffi Dreha-Kulaczewski,[2] Janusz Wiśniewski,[1] Przemysław Duda,[1] Andreas Ohlenbusch,[2] Brenda Huppke,[2,3] Marco Henneke,[2] Wolfgang Höhne,[4] Janine Altmüller,[4] Holger Thiele,[4] Peter Nürnberg,[4] Dariusz Rakus,[1] Jutta Gärtner[2] and Peter Huppke[2,3]

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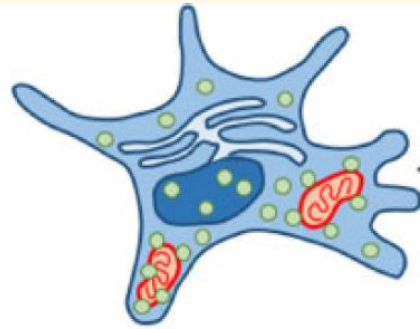
Leukodystrophies are genetic disorders of cerebral white matter that almost exclusively have a progressive disease course. We became aware of three members of a family with a disorder characterized by a sudden loss of all previously acquired abilities around 1 year of age followed by almost complete recovery within 2 years. Cerebral MRI and myelin sensitive imaging showed a pronounced demyelination that progressed for several months despite signs of clinical improvement and was followed by remyelination. Exome sequencing did not-identify any mutations in known leukodystrophy genes but revealed a heterozygous variant in the *FBP2* gene, c.343G>A, p. Val115Met, shared by the affected family members. Cerebral MRI of other family members demonstrated similar white matter abnormalities in all carriers of the variant in *FBP2*. The *FBP2* gene codes for muscle fructose 1,6-bisphosphatase, an enzyme involved in gluconeogenesis that is highly expressed in brain tissue. Biochemical analysis showed that the variant has a dominant negative effect on enzymatic activity, substrate affinity, cooperativity and thermal stability. Moreover, it also affects the non-canonical functions of muscle fructose 1,6-bisphosphatase involved in mitochondrial protection and regulation of several nuclear processes. In patients' fibroblasts, muscle fructose 1,6-bisphosphatase shows no colocalization with mitochondria and nuclei leading to increased reactive oxygen species production and a disturbed mitochondrial network. In conclusion, the results of this study indicate that the variant in *FBP2* disturbs cerebral energy metabolism and is associated with a novel remitting leukodystrophy.

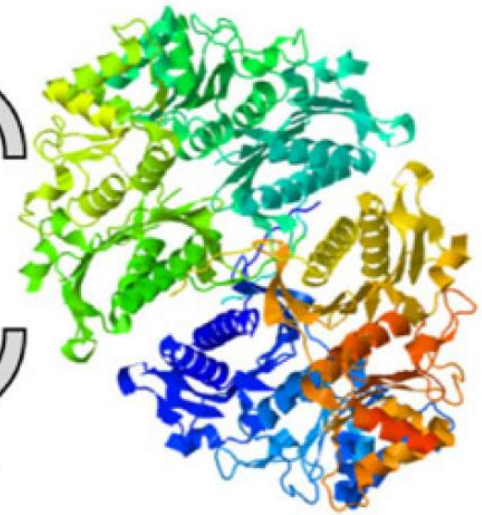
- Üç indeks hasta,
- 10-13 aylıkken ateşli bir hastalık sırasında tüm öğrenilmiş yeteneklerini kaybetmiş
- Akut epizodu, kademeli bir iyileşme evresi ve 1-2 yıl içinde normal gelişim durumuna ulaşma
- Akut fazda difüzyon ağırlıklı manyetik rezonans görüntüleme, etkilenen beyaz maddede kısıtlı difüzyon göstererek metabolik krizle uyumlu sitotoksik ödemi
- Beyaz cevherde artmış laktat
- Miyelinde akut evrede azalma, ardından kademeli bir artış ve beyaz madde miyelininde neredeyse normalleşme
- Görüntüleme verileri ve klinik seyir, 1-2 yıllık bir süre içinde büyük çaplı demiyelinizasyon ve ardından remiyelinizasyon ile uyumlu
- Bu hastaların ailelerindeki toplam 5 mutasyon taşıyıcısına yapılan MRG'de hasta çocuklarının görüntülerine benzer gliotik sekel lezyonlar

- Change of subcellular localization of the protein;
- Decrease of mitochondrial membrane potential;
- Increased ROS production;
- Overload of protein degradation systems.

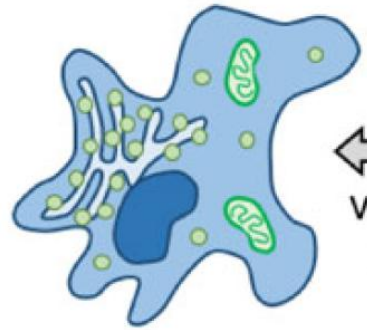
ROS – Reactive oxygen species



Wild type protein



Fructose 1,6-bisphosphatase 2 (FBP2)

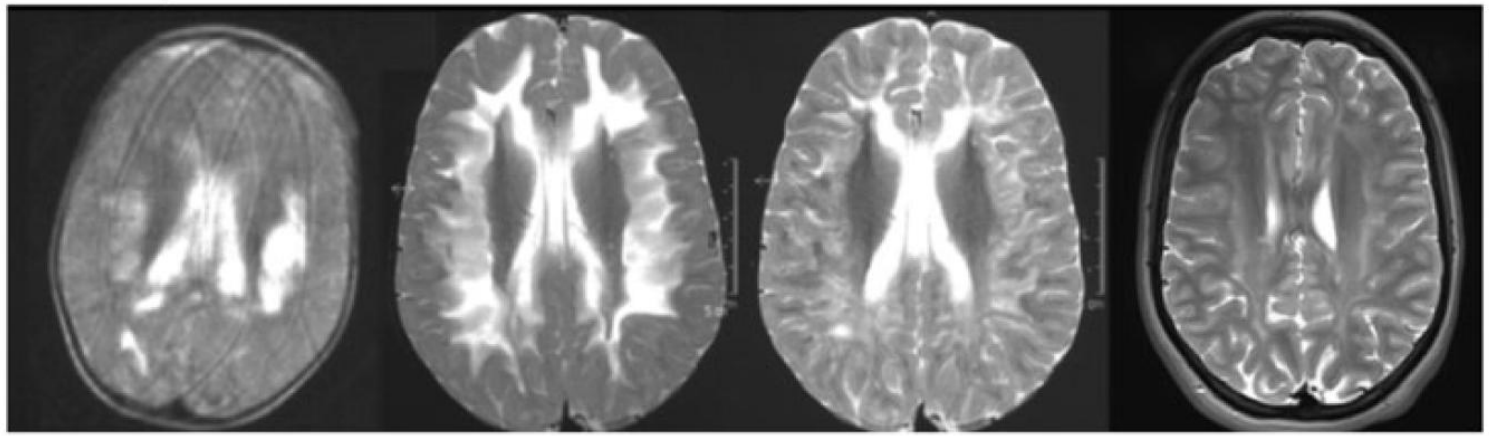


Val115Met variant

Loss of all developed abilities

Continuous improvement

Slight abnormalities



11 months *21 months* *32 months* *24 years*

- V115M-FBP2 varyantının patojenitesini değerlendirmek için, varyantın kinetik özelliklerini ve stabilitesini içeren enzimatik fonksiyonu araştırılmış,
- V115M-FBP2'nin aktivitesinin, termal stabilitesinin ve substrat afinitesinin azaldığı bulunmuş
- FBP2'nin ifade edildiği ancak FBP1'in ifade edilmediği beyindeki glukoneogenezin rolü tam olarak anlaşılmamıştır, ancak fizyolojik ve patolojik koşullar altında yerel enerji metabolizmasının önemli bir parçası olduğuna dair kanıtlar vardır.
- Karaciğer enzimi FBP1'in fruktoz-1,6-bisfosfat eksikliğinde, hipoglisemi ve laktik asidoz ile akut ataklar genellikle ateşli enfeksiyonlar tarafından tetiklenir.
- Burada açıklanan üç indeks hastasında da şiddetli kriz ateşli bir enfeksiyonu takip etmiş ve akut fazda MRS'de beyaz maddede laktat yükselmiş. Bu bulgular, kusurlu glukoneogenezin patofizyolojiye katkıda bulunabileceğini göstermektedir.
- Miyelin sentezi çok enerji tüketen bir süreç olduğundan, oligodendrositler yaşamın ilk yılının sonundaki yoğun miyelinleşme evresinde bu tür bir kusura karşı özellikle savunmasız olabilirler.

- Kendiliğinden iyileşen dört lökodistrofi tanımlanmıştır
- Mekanosensitif bir iyon kanalını kodlayan TMEM63A genindeki varyantlara sahip hastalar, merkezi sinir sisteminin hipomiyelinizasyonu ile ilişkili olarak bebeklik döneminde konjenital nistagmus ve motor gecikme ile başvururlar. Bebeklik döneminde miyelin eksikliği düzelir ve klinik seyir olumlu olur.
- Plazma membran Na + /dikarboksilat kotransporter 3'ü kodlayan SLC13A3 genindeki varyantlar , ateşli hastalık sırasında geri dönüşümlü bir lökensefalopati ile ilişkilendirilmiştir. Krizden günler sonra klinik iyileşme gözlemlenmiş ve MR değişiklikleri normale dönmüştür.
- GLIALCAM'deki resesif mutasyonlar, subkortikal kistlerle birlikte klasik bir megaensefalik lökensefalopatiye neden olur. Bununla birlikte, aynı gendeki otozomal dominant mutasyonlar, iyileşen bir fenotiple ilişkilendirilmiştir.
- Son olarak, mitokondriyal [Fe-S] protein montajında rol alan bir proteini kodlayan FDX2'de mutasyon bulunan iki ailede yakın zamanda lökensefalopatinin kısmi düzelmesi bildirilmiş ancak klinik seyir ilerleyici kalmıştır.

Kaynaklar

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