Vaka Sunumu

S.G.A.

S.G.A.

- **Şikayet**

- 3,5 aylık kız bebek
- Kusma, beslenememe, bilinç bozukluğu
- Solunum durması

S.G.A.

- **Hikaye**

- Öncesinde herhangi bir şikayeti olmayan hastanın son 1-2 gündür kusmaları ve beslenememesi olmuş,
- Çocuk acil poliklinik başvurusunda solunum arresti gelişmiş ve entübe edilerek çocuk yoğun bakım ünitesine alınmış.

S.G.A.

- **Özgeçmiş**

- G1P1Y1 miad 2950 gr C/S
- Prenatal, natal, postnatal dönemde herhangi bir sorun olmamış
- Baş tutması yeni başlamış, anne sütü ile besleniyor

- **Soygeçmiş**

- Anne 27 yaş sağlıklı, üniv mezunu
- Baba 29 yaş sağlıklı, üniv mezunu
- Akrabalık yok, köyler farklı Bursa- Bilecik
- Ailede bilinen ciddi hastalık hikayesi yok

S.G.A.

- **Fizik Muayene**

- Vücut Ağırlığı: 5.8 kg (25-50p)
- Boy: 57 cm (3-10p)
- Baş Çevresi: 39 cm (10p)

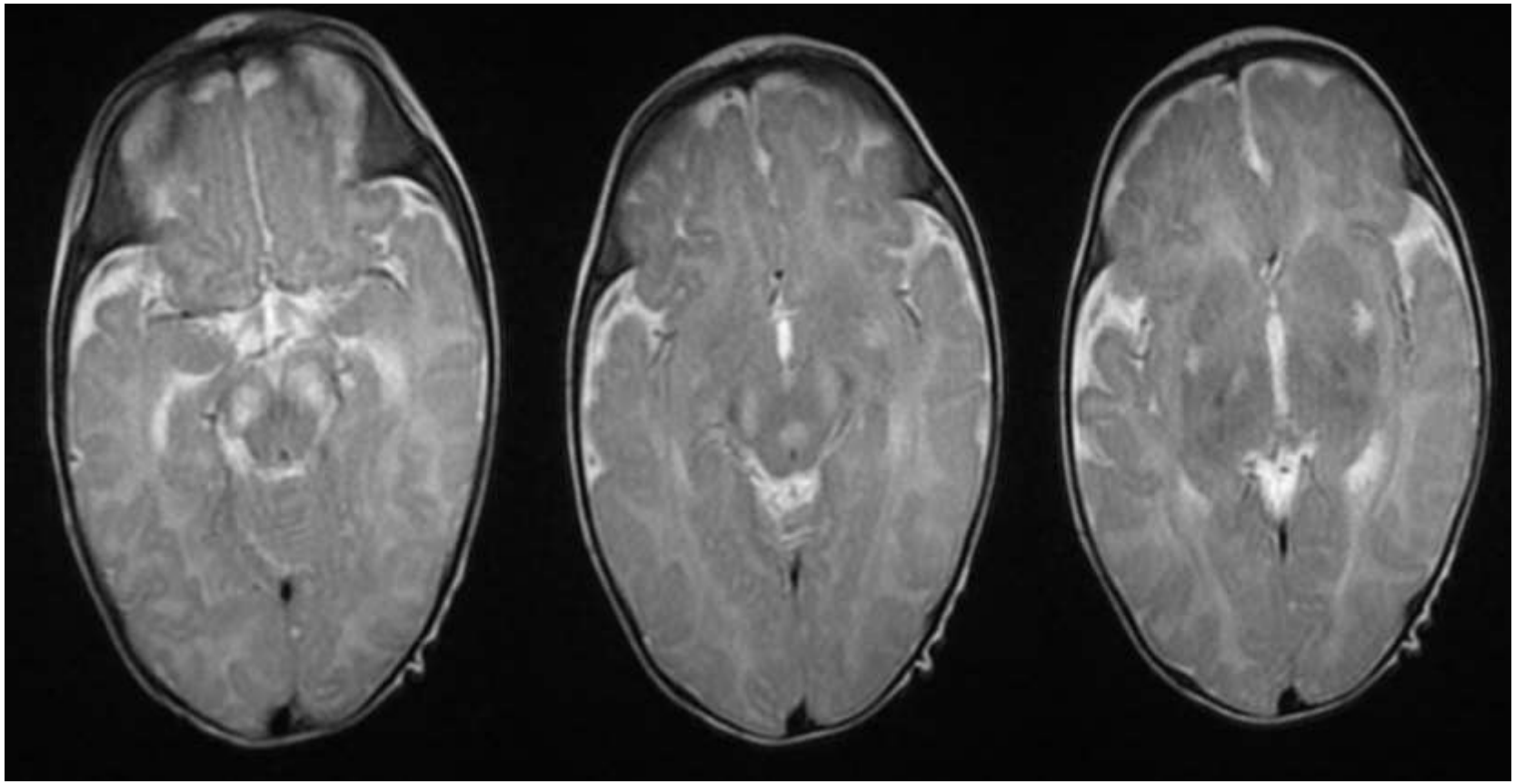
- Entübe
- Kalp sesleri normal, ek ses ve üfürüm yok
- Batın rahat, organomegali saptanmadı.

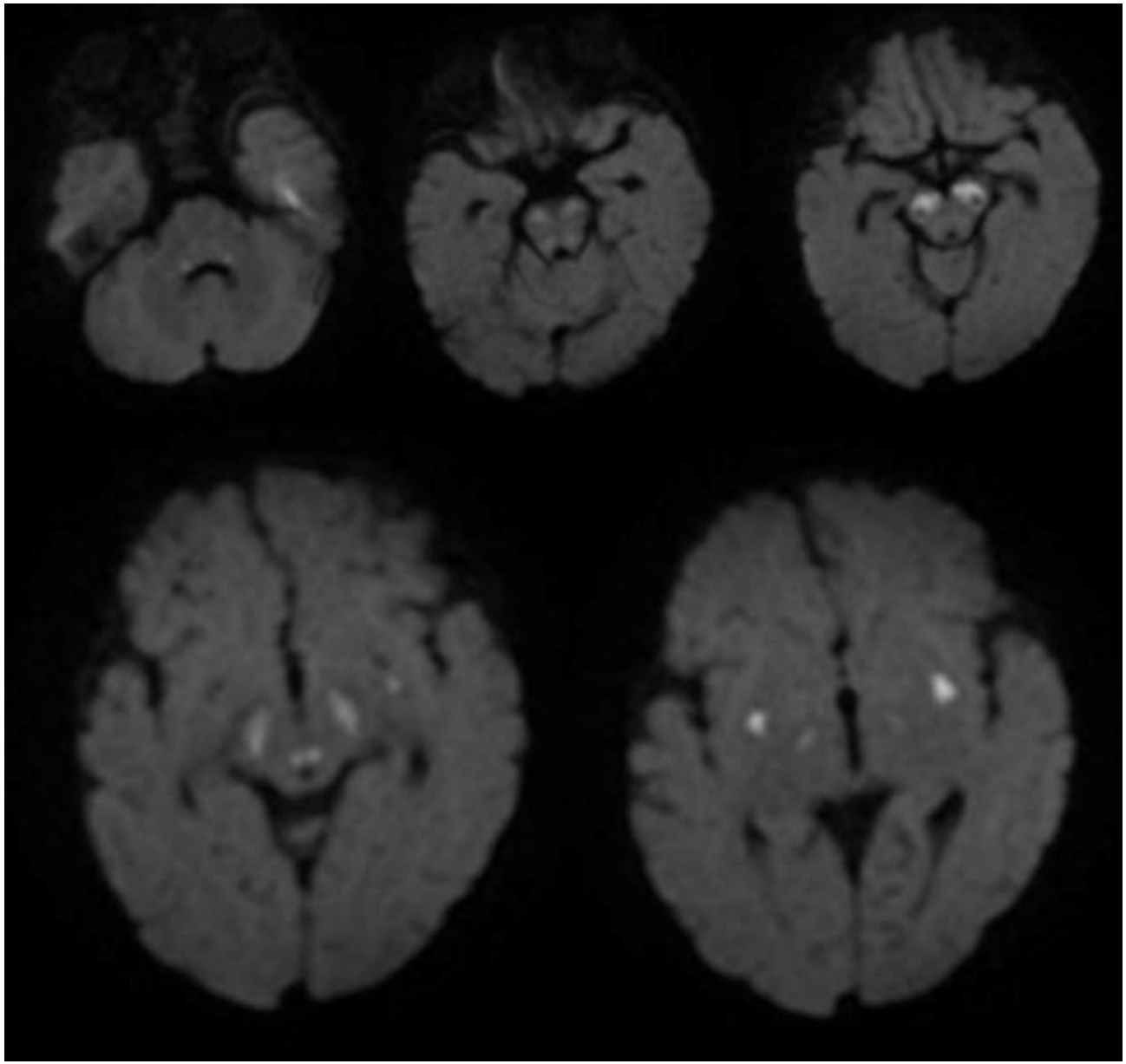
S.G.A.

- **<u>Nörolojik Muayene</u>**

- Bilinç Kapalı, Hipoaktif,
- Pupiller İzokorik Dır /idır:++/++
- Göz Hareketleri Değerlendirilemedi
- Nistagmus Yok
- Fasikülasyon Yok
- Kas Gücü: Ağrılı Uyaranla Ekstremiteyi Hafif Çekiyor
- Tonus Hipotonik
- Dtr Normoaktif, Klonus Yok

S.G.A.





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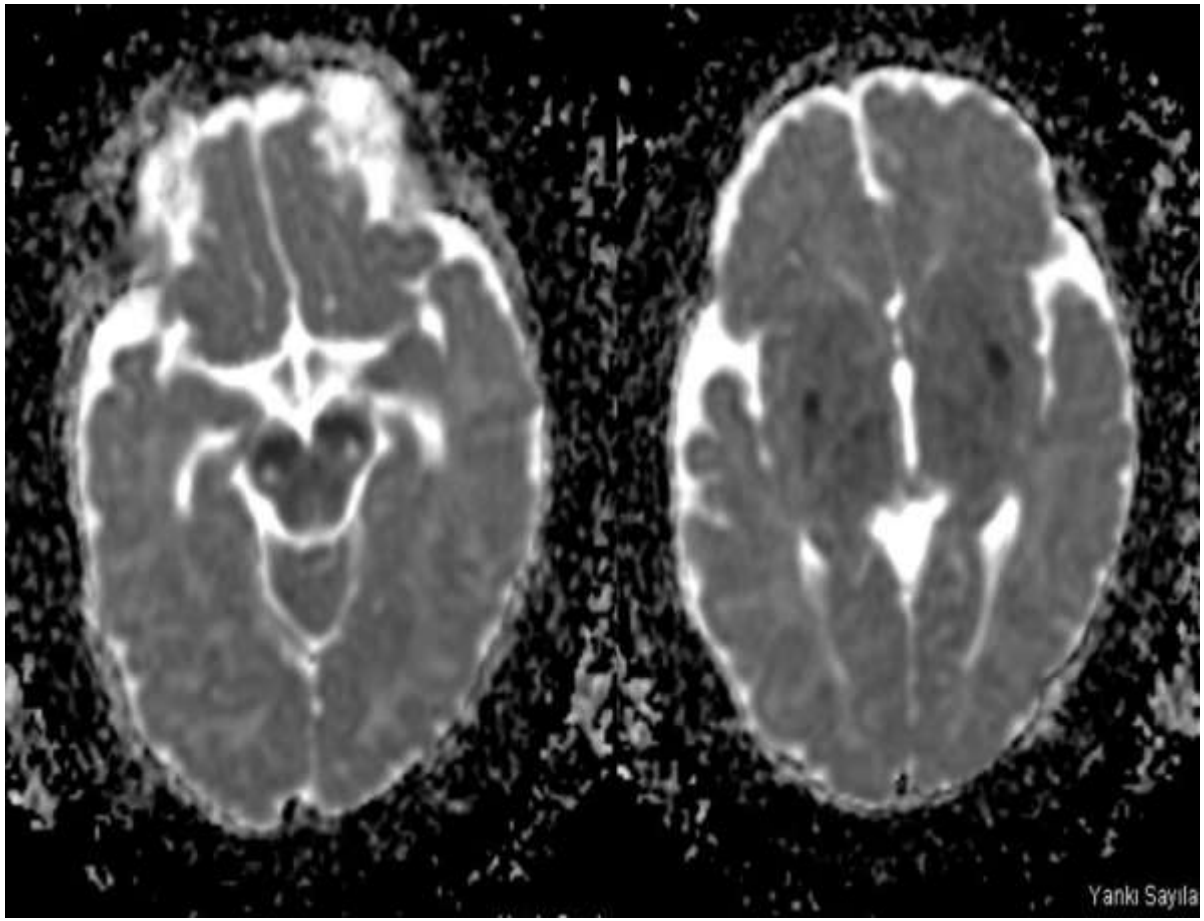

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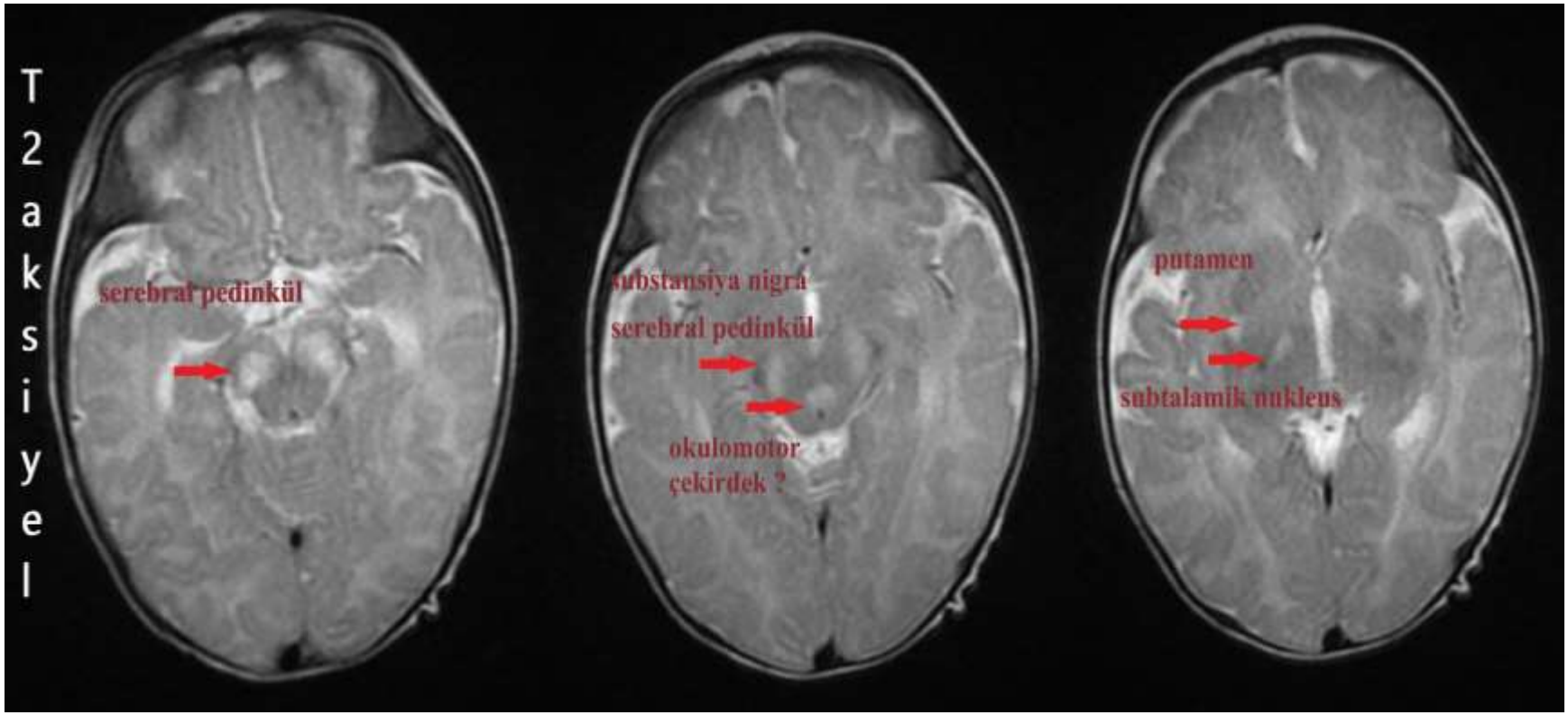
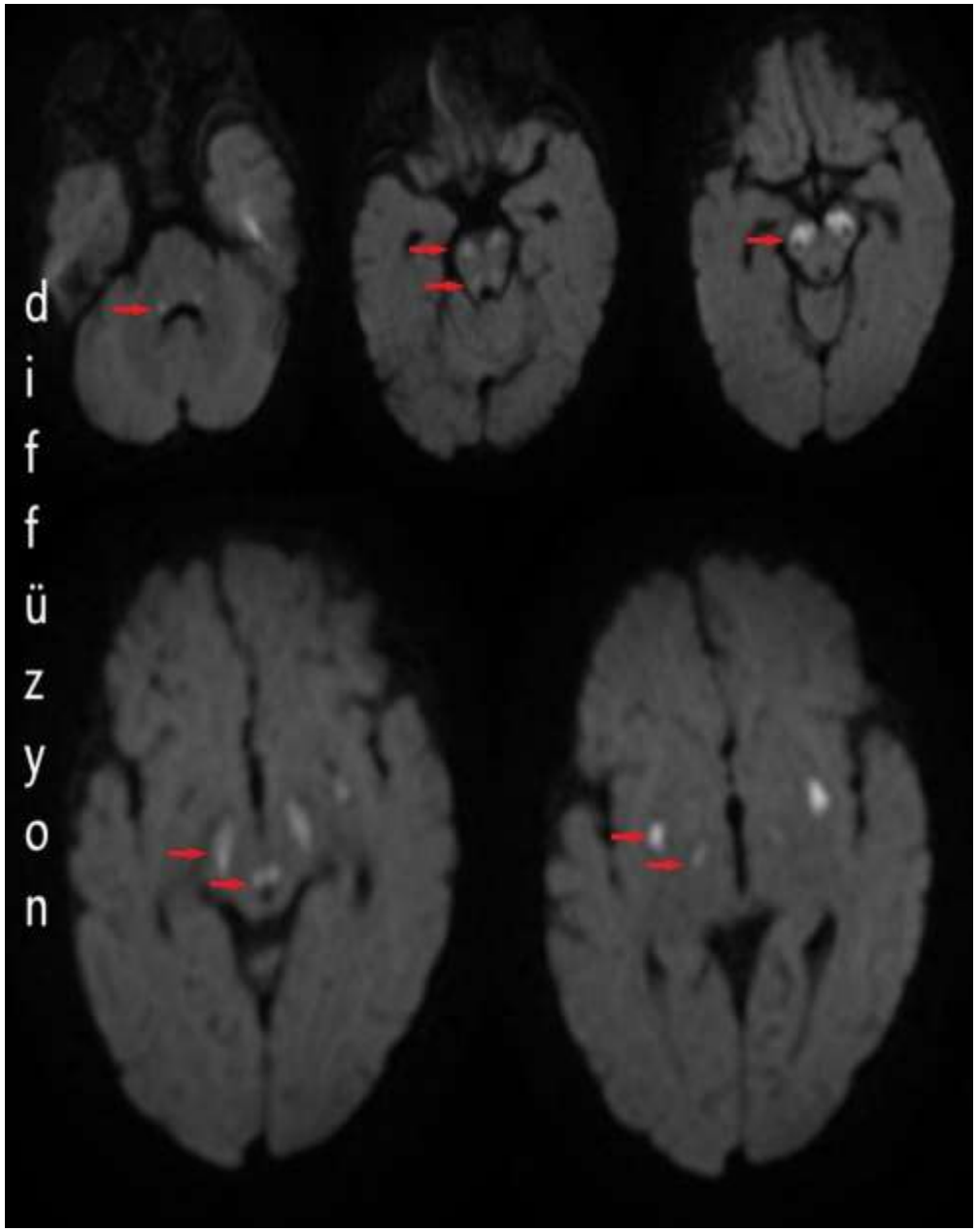
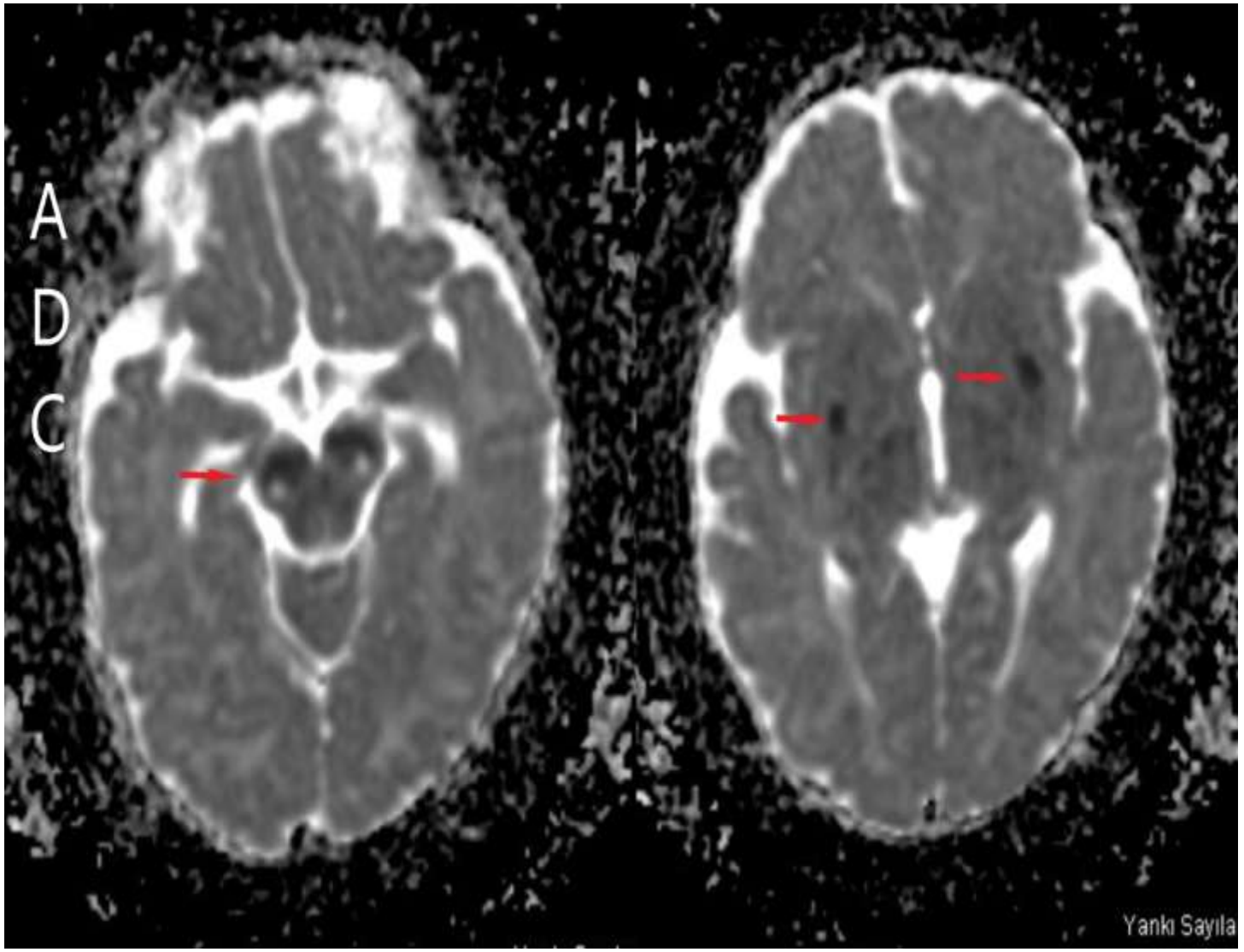

T2 aksiyel
serebral pedinkül
substansiya nigra
serebral pedinkül
okulomotor
çekirdek ?
putamen
subtalamik nukleus


difüzyon


A
D
C
Yankı Sayıla

Kan gazı: pH 7.11
pCO2: 49
Lac: 11(0.5-2)
HCO3: 9
Anyon Gap: 24
Kan şekeri: 99 mg/dl
Parmak ucu keton: 0.2
TİT: keton neg
Amonyak: 95 mmol/L

Hemogram: Normal
Biyokimya: AST/ALT: 85/97
CK: 211
Ürik asit, kolesteroller, LDH normal

CRP: Normal

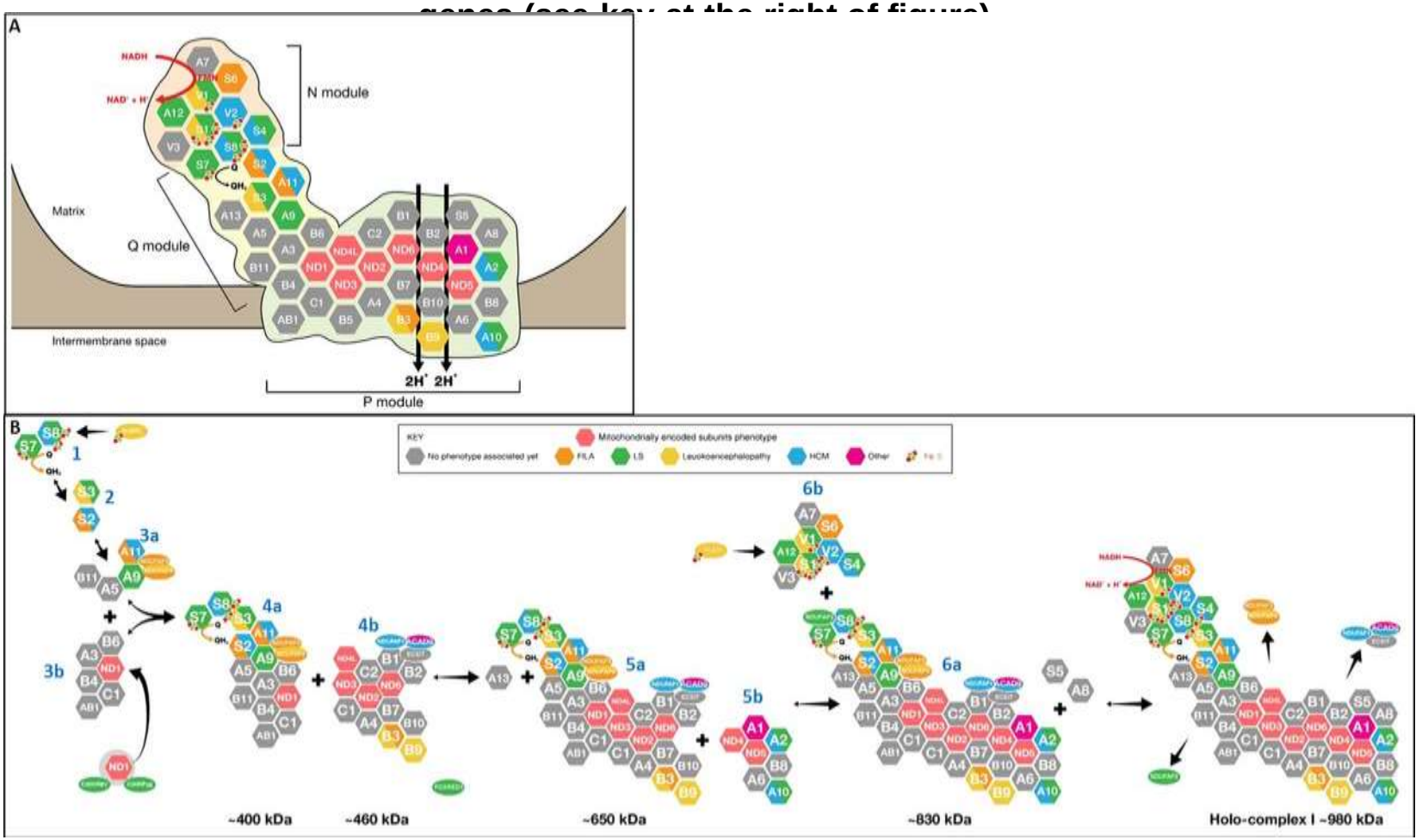
TANDEM Asil karnitin profili: Normal
Kan aminoasit kromatografisi:
Alanin: 1100 (N:143-469)
İdrar organik Asit:
İleri düzeyde Laktik asit ve Piruvik asit atılımı
Fumarik Asit, Malik asit, Etilmalonik asit 2-3 kat yüksekliği

Göz dibi muayenesi: Normal
Ekokardiyografi: Normal

S.G.A.

- **Tanı:**
- **NDUFS4** geninde
- p.Arg106* (c.316C>T) ve p.Lys154Asnfs* (c.462delA)
- Birleşik heterozigot
- Mitochondrial Complex I deficiency (MIM NO:252010)

Structure and assembly of human mitochondrial respiratory chain complex I. (A) Structure of complex I, showing the 45 subunits (seven encoded by mitochondrial DNA and 38 by nuclear genes), colour-coded according to the clinical phenotype(s) associated with mutations of these genes (see key at the right of figure)



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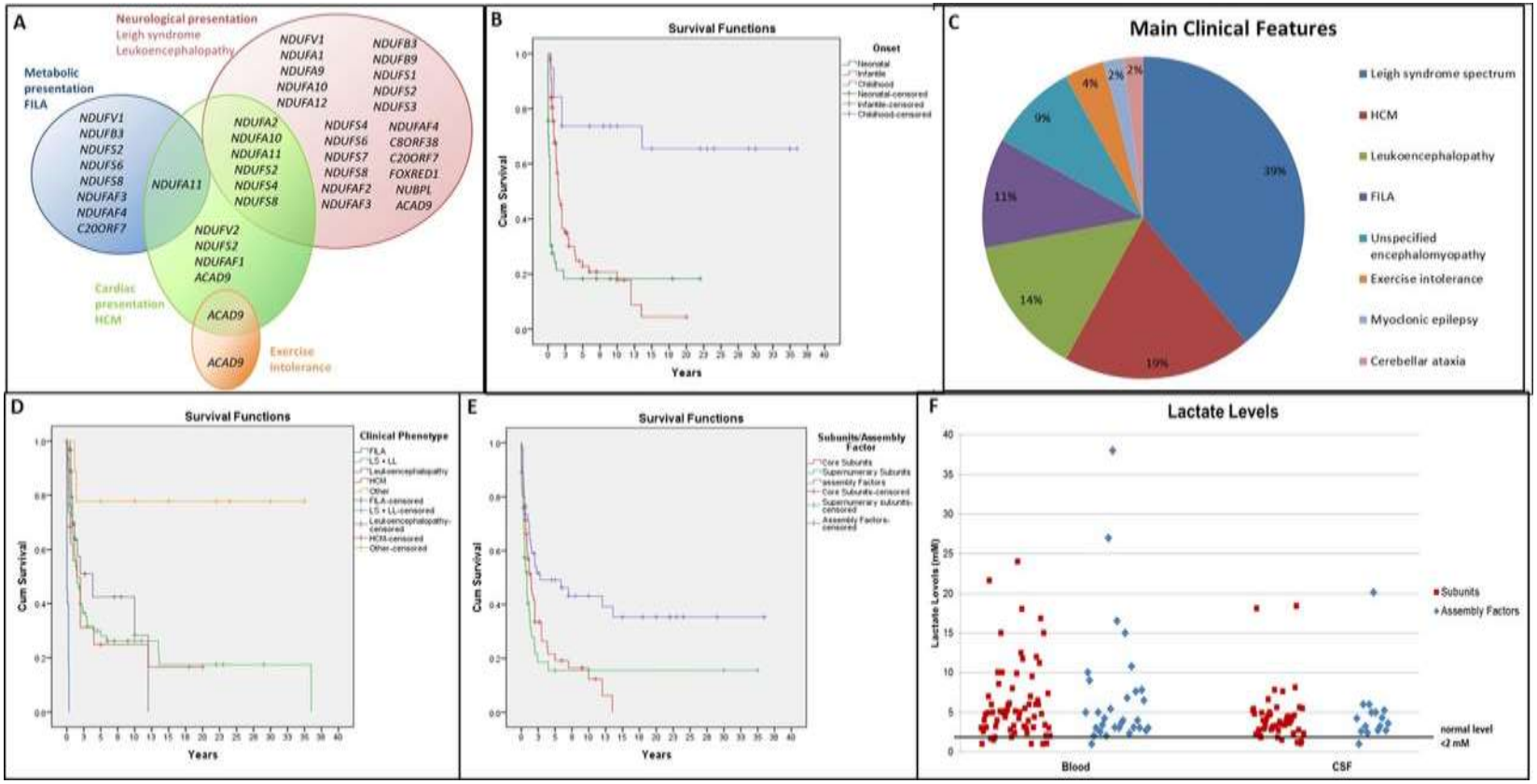
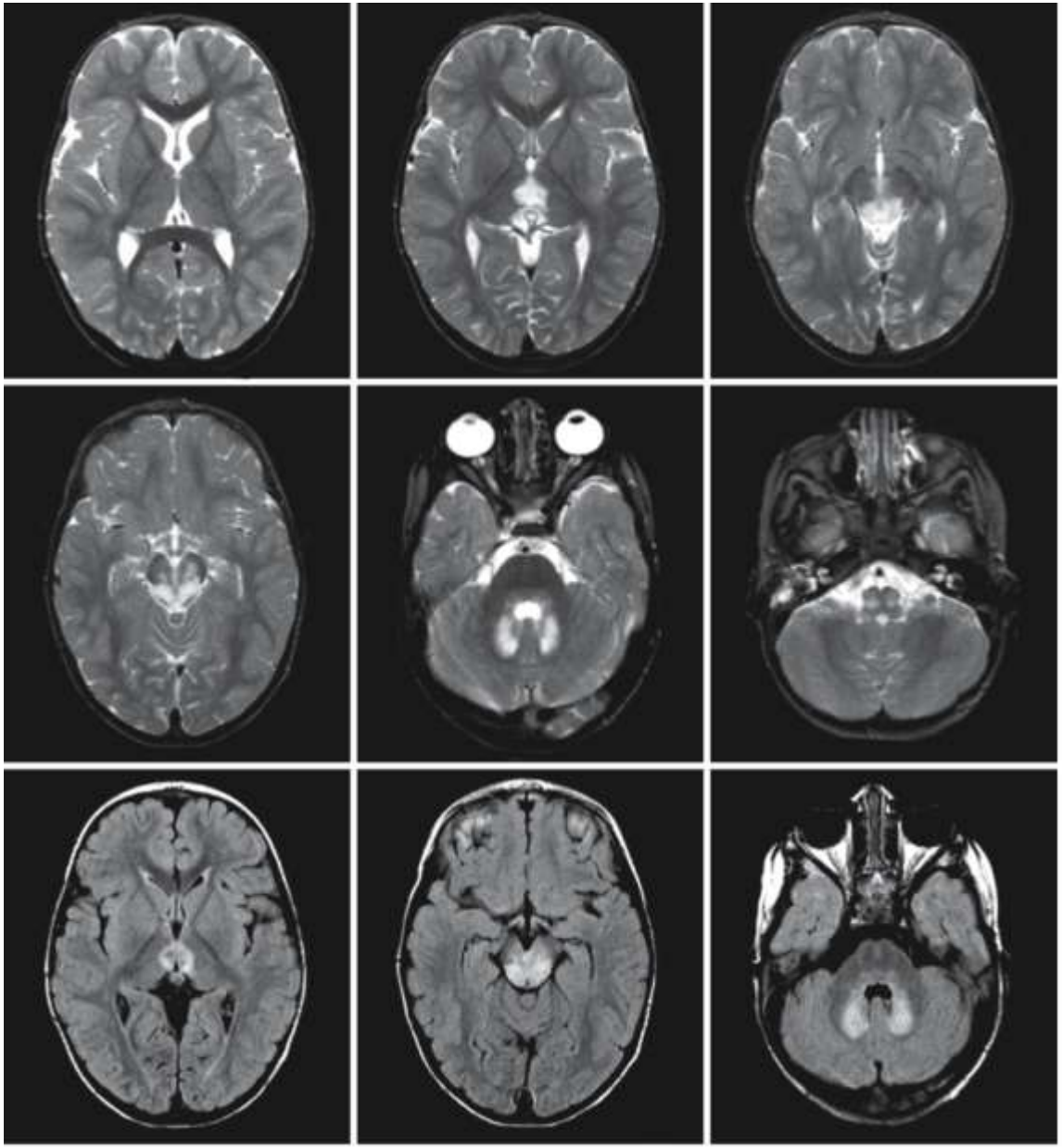
Genotype to phenotype correlations in nuclear-encoded complex I deficiency.



Elisa Fassone, and Shamima Rahman J Med Genet 2012;49:578-590



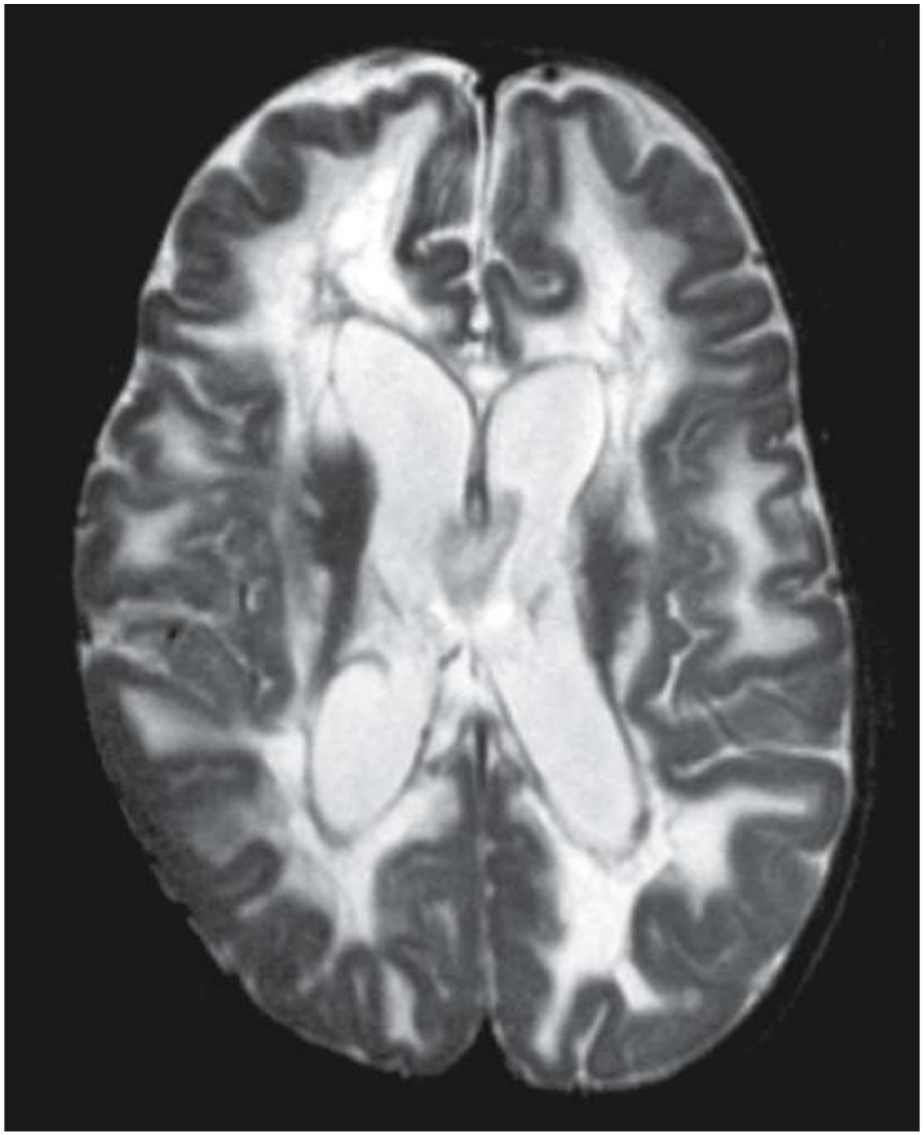


Fig. 28.4. A 1-year-old girl with complex I deficiency related

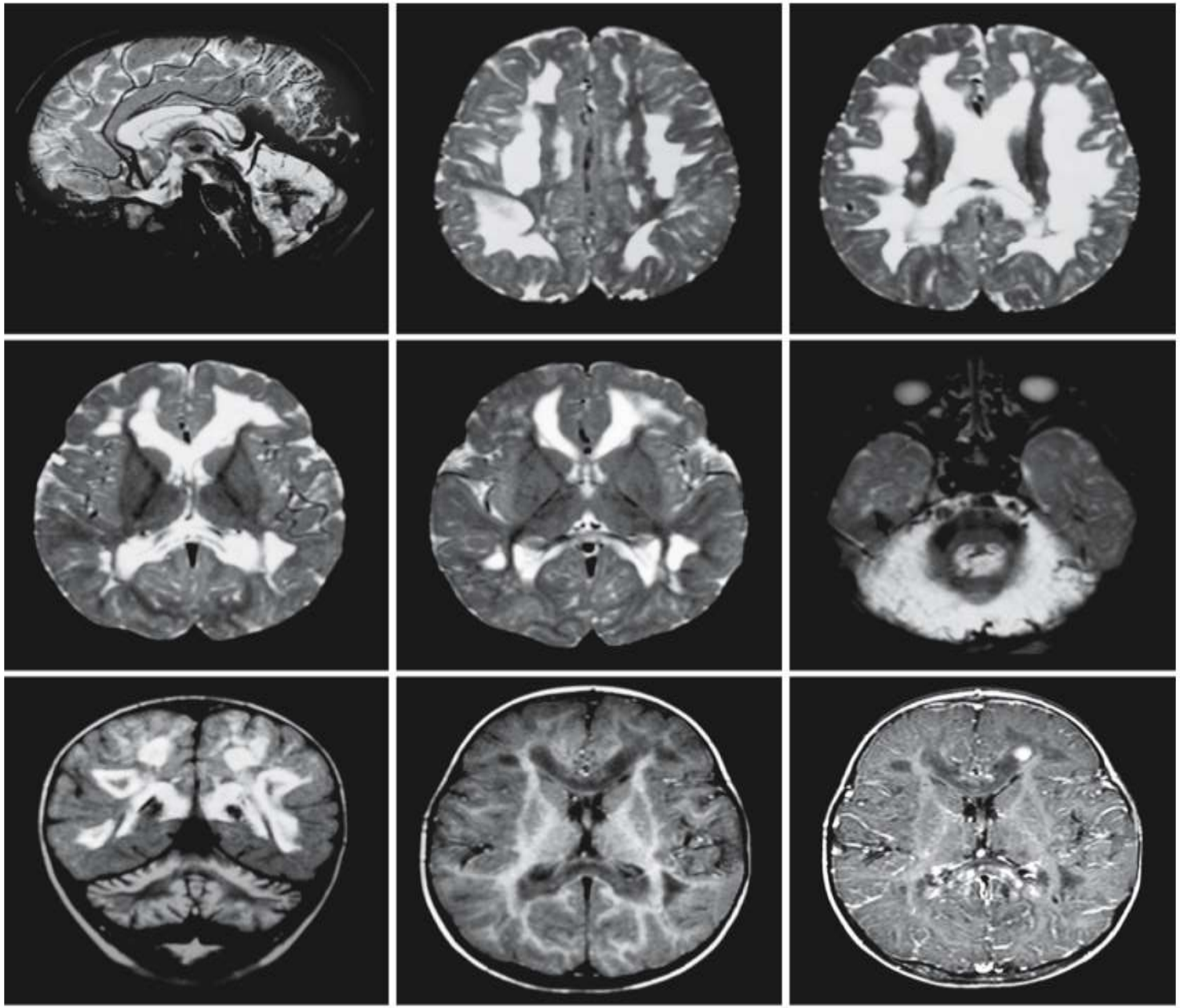


Fig. 28.5. A 19-month-old boy with isolated complex I defi- fusely abnormal. The T_1-weighted images without (*third row,*

REVIEW

Complex I deficiency: clinical features, biochemistry and molecular genetics

Elisa Fassone,[1] Shamima Rahman[1,2,3]

► Additional data are published online only. To view this file please visit the journal online (http://jmg.bmj.com).
10.1136/jmedgenet-2012-101158

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ABSTRACT

Complex I deficiency is the most frequent mitochondrial disorder presenting in childhood, accounting for up to 30% of cases. As with many mitochondrial disorders, complex I deficiency is characterised by marked clinical and genetic heterogeneity, leading to considerable diagnostic challenges for the clinician, not least because of the involvement of two genomes. The most prevalent clinical presentations include Leigh syndrome, leukoencephalopathy and other early-onset neurodegenerative disorders; fatal infantile lactic acidosis; hypertrophic cardiomyopathy; and exercise intolerance. Causative genetic defects may involve the seven mitochondrial-encoded or 38 nuclear-encoded subunits of the enzyme, or any of an increasing number of assembly factors implicated in the correct biosynthesis of complex I within the inner mitochondrial membrane. In this review, we discuss recent advances in knowledge of the structure, function and assembly of complex I and how these advances, together with new high-throughput genetic screening techniques, have translated into improved genetic diagnosis for affected patients and their families. Approximately 25% of cases have mitochondrial DNA mutations, while a further ~25% have mutations in a nuclear subunit or in one of nine known assembly factors. We also present a systematic review of all published cases of nuclear-encoded complex I deficiency, including 117 cases with nuclear subunit mutations and 56 with assembly factor mutations, and highlight clinical, radiological and biochemical clues that may expedite genetic diagnosis.

INTRODUCTION

Complex I (nicotinamide adenine dinucleotide (NADH):ubiquinone oxidoreductase, Enzyme Commission number EC 1.6.5.3) is the first and largest enzyme of the mitochondrial respiratory chain (RC) and oxidative phosphorylation (OXPHOS) systems, and plays critical roles in transferring electrons from reduced NADH to coenzyme Q$_{10}$ (CoQ$_{10}$, ubiquinone) and in pumping protons to maintain the electrochemical gradient across the inner mitochondrial membrane. This electrochemical gradient, generated by complexes I, III and IV is subsequently harnessed by complex V (ATP synthase) to synthesise ATP from ADP and inorganic phosphate. Complex I is also the major site for the generation of reactive oxygen species (ROS), which are increasingly recognised to be important signalling molecules determining the health and fate of the mitochondrion and of the whole cell.

Isolated deficiency of complex I is the most commonly identified biochemical defect in childhood-onset mitochondrial disease, accounting for approximately a third of all cases of OXPHOS disorders.[1] Complex I deficiency is clinically heterogeneous but the majority of affected individuals develop symptoms during the first year of life and have a rapidly progressive disease course, resulting in a fatal outcome in childhood. However, clinical presentations may vary, ranging from fatal neonatal lactic acidosis or infantile-onset Leigh syndrome, childhood-onset mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome and, in some cases, adult-onset encephalomyopathic syndromes of variable severity. Presentation with single organ involvement is also recognised, for example, isolated hypertrophic cardiomyopathy (HCM) or Leber's hereditary optic neuropathy (LHON).

Inherited complex I deficiency can result from mutations in either mitochondrial DNA (mtDNA) or nuclear-encoded structural subunits of the enzyme or from mutation of any of a rapidly expanding number of nuclear-encoded complex I assembly factors. To date, genetic defects have been reported for all seven mtDNA-encoded complex I subunits, 17 of the 38 nuclear-encoded subunits and nine assembly factors. Pathogenic mtDNA mutations may be maternally inherited or sporadic, while most nuclear-encoded complex I defects are inherited in autosomal recessive traits, although a small number of X-linked defects have been reported.

In this review, we discuss the structure, function and assembly of the enzyme, report the findings of a systematic review of the clinical features of 173 published patients with nuclear-encoded complex I defects, including clinical and radiological clues that may aid genetic diagnosis, and consider potential approaches to developing treatments for these devastating disorders.

STRUCTURE AND FUNCTION OF COMPLEX I

The L-shaped structure of complex I was initially revealed by electron microscopy; further detail was subsequently provided by x-ray crystallography studies of the enzyme in the bacterium *Thermus thermophilus* and the fungus *Yarrowia lipolytica*, which demonstrated the relative positions of the subunits in these organisms.[2–4] Efforts are underway to determine the positions of the subunits in the mammalian enzyme by crystallising purified complex I from bovine heart. Human complex I is very similar to bovine complex I and consists of 45 different subunits (figure 1A),[5] 14 of which are necessary for catalytic function and are conserved in all species that have a complex I including

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European Journal of Human Genetics (2011) 19, 769–775

www.nature.com/ejhg

ARTICLE

Respiratory chain complex I deficiency caused by mitochondrial DNA mutations

Helen Swalwell[1], Denise M Kirby[2], Emma L Blakely[1], Anna Mitchell[1], Renato Salemi[2,6], Canny Sugiana[2,3,7], Alison G Compton[2], Elena J Tucker[2,5], Bi-Xia Ke[2], Phillips J Lamont[4], Douglass M Turnbull[1], Robert McFarland[1], Robert W Taylor[1] and David R Thorburn*[,2,3,5]

Defects of the mitochondrial respiratory chain are associated with a diverse spectrum of clinical phenotypes, and may be caused by mutations in either the nuclear or the mitochondrial genome (mitochondrial DNA (mtDNA)). Isolated complex I deficiency is the most common enzyme defect in mitochondrial disorders, particularly in children in whom family history is often consistent with sporadic or autosomal recessive inheritance, implicating a nuclear genetic cause. In contrast, although a number of recurrent, pathogenic mtDNA mutations have been described, historically, these have been perceived as rare causes of paediatric complex I deficiency. We reviewed the clinical and genetic findings in a large cohort of 109 paediatric patients with isolated complex I deficiency from 101 families. Pathogenic mtDNA mutations were found in 29 of 101 probands (29%), 21 in *MTND* subunit genes and 8 in mtDNA tRNA genes. Nuclear gene defects were inferred in 38 of 101 (38%) probands based on cell hybrid studies, mtDNA sequencing or mutation analysis (nuclear gene mutations were identified in 22 probands). Leigh or Leigh-like disease was the most common clinical presentation in both mtDNA and nuclear genetic defects. The median age at onset was higher in mtDNA patients (12 months) than in patients with a nuclear gene defect (3 months). However, considerable overlap existed, with onset varying from 0 to >60 months in both groups. Our findings confirm that pathogenic mtDNA mutations are a significant cause of complex I deficiency in children. In the absence of parental consanguinity, we recommend whole mitochondrial genome sequencing as a key approach to elucidate the underlying molecular genetic abnormality.
European Journal of Human Genetics (2011) **19**, 769–775; doi:10.1038/ejhg.2011.18; published online 2 March 2011

Keywords: respiratory chain; complex I; mitochondrial DNA; mutation; genetic counselling

INTRODUCTION

Isolated complex I deficiency is the most frequently observed mitochondrial respiratory chain disorder, and is associated with a wide range of clinical presentations, including marked and often fatal lactic acidosis, cardiomyopathy, leukoencephalopathy, pure myopathy and hepatopathy with tubulopathy.[1–3] Complex I deficiency is one of the most common mitochondrial disorders of childhood; onset is usually early and death often occurs within the first year of life.[4–7]

Defining the molecular basis of complex I deficiency is a difficult task, not least because of the dual genetic control governing the correct assembly and function of complex I, but also as the largest complex in the mitochondrial respiratory chain, it is also the most intricate. Complex I is composed of 45 subunits,[8] 7 of which are encoded by mitochondrial DNA (mtDNA), and the remaining 38 are nuclear encoded. Moreover, a number of proteins are involved in the correct processing and assembly of complex I, the total number of which as yet remains unknown.[9]

To date, pathogenic mutations in structural complex I proteins, leading to complex I deficiency and associated with a diverse phenotype, have been identified in 21 nuclear genes; 11 of the 36 autosomal genes encoding complex I subunits (namely *NDUFS1*, *NDUFS2*, *NDUFS3*, *NDUFS4*, *NDUFS6*, *NDUFS7*, *NDUFS8*, *NDUFV1*, *NDUFV2*, *NDUFA2* and *NDUFA11*), 1 of the 2 chromosome X genes encoding complex I subunits (*NDUFA1*) and 9 autosomal genes encoding proteins involved in complex I assembly, namely *NDUFAF1* (*CIA30*), *NDUFAF2* (*B17.2L*), *NDUFAF3*, *NDUFAF4*, *C6orf66*, *C20orf7*, *NUBPL*, *FOXRED1* and *ACAD9*.[10–16] Mutations in nuclear genes involved in mtDNA maintenance, in particular *POLG*, which encodes the catalytic subunit of the mitochondrial polymerase γ, may also cause isolated complex I deficiency in patients with Alpers' syndrome.[17] Equally, mutations have been identified in all seven of the mtDNA genes encoding subunits of complex I,[12] and also in mtDNA tRNA (mt-tRNA) genes, particularly mitochondrial tRNA$^{Leu(UUR)}$.[1]

The importance of mtDNA mutations as a potential molecular aetiology for complex I deficiency was therefore not in doubt, but thus far their prevalence remained unclear. Indeed, it was previously believed that complex I deficiency due to mtDNA mutations accounted for only 5–10% of paediatric complex I deficiency cases.[18,19] Recent screening of mitochondrial complex I subunit genes has shown mutations in mtDNA accounting for a much higher number of cases,[14,20] and therefore, its screening is an essential step in the genetic diagnosis of complex I deficiency. Previous studies

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