EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 16 (2012) 10–14

Official Journal of the European Paediatric Neurology Society

Original article

Alternating hemiplegia of childhood: Metabolic studies in the largest European series of patients

Carmen Fons [a], *Jaume Campistol* [a,*], *Eleni Panagiotakaki* [c], *Melania Giannotta* [d], *Alexis Arzimanoglou* [c,l], *Giuseppe Gobbi* [d], *Brian Neville* [e], *Friedrich Ebinger* [f], *Soňa Nevšímalová* [g], *Laura Laan* [h], *Paul Casaer* [i], *Georg Spiel* [j], *Miriam Ninan* [e], *Guenter Sange* [j], *Rafael Artuch* [b], *Tsveta Schyns* [k], *Rosaria Vavassori* [k], *Dominique Poncelin* [k], *the ENRAH Consortium* [k,m]

[a] *Department of Child Neurology, Sant Joan de Déu Hospital, Barcelona University (UB), CIBERER, Spain*
[b] *Department of Clinical Biochemistry, Sant Joan de Déu Hospital, Barcelona University (UB), CIBERER, Spain*
[c] *Institute for Children and Adolescents with Epilepsy (IDEE), Hôpital Femme Mère Enfant, University Hospitals of Lyon (HCL), France*
[d] *Child Neurology Unit, Department of Neuroscience, Maggiore Hospital, Bologna, Italy*
[e] *Institute of Child Health, UCL, London, UK*
[f] *Department of Child Neurology, Heidelberg University Hospital, Germany*
[g] *Department of Neurology, Charles University, 1st Faculty of Medicine and Teaching Hospital, Prague, Czech Republic*
[h] *Department of Neurology, K5Q, Leiden University Medical Center, Leiden, Netherlands*
[i] *Department of Child Neurology, University Hospital Gasthuisberg, Leuven, Belgium*
[j] *Department of Neurology and Psychiatry of Children and Adolescents, General Hospital, Klagenfurt, Austria*
[k] *The ENRAH Consortium, Austria*
[l] *Inserm U821 and TIGER Research Group, Lyon, France*

ARTICLE INFO

Article history:
Received 25 January 2011
Received in revised form
5 August 2011
Accepted 21 August 2011

Keywords:
Alternating hemiplegia
Mitochondrial encephalopathy

ABSTRACT

Alternating hemiplegia of childhood (AHC) is a rare disorder with diagnosis based on clinical criteria, as no laboratory, neuroradiological or genetic markers are currently available. The pathogenic mechanisms are still an enigma. Some hypotheses have been proposed such as hemiplegic migraine variant, epileptic mechanism, channelopathy and mitochondrial disorder, but none of these has been confirmed. Our aim was to analyze the results of metabolic studies performed on a series of 157 European patients who fulfilled diagnostic criteria for AHC. We tried to find a common metabolic abnormality, related with AHC. We did not find significant abnormalities in basic metabolic screening, at different ages. Neurotransmitters in cerebrospinal fluid ($n = 26$) were normal in all of the patients. Mitochondrial respiratory chain enzyme activities were analyzed in 19 muscle biopsies; in

* *Corresponding author*. Department of Pediatric Neurology, Sant Joan de Déu Hospital, University of Barcelona, Passeig Sant Joan de Déu, 2, 08950 Esplugues, Barcelona, Spain. Tel.: +34 93 280 4000; fax: +34 93 203 3959.
E-mail address: campistol@hsjdbcn.org (J. Campistol).

[m] **The ENRAH Consortium:** Arzimanoglou Alexis (France), Campistol Jaume (Spain), Casaer Paul (Belgium), Ebinger Friedrich (Germany), Fons Carmen (Spain), Giannotta Melania (Italy), Gobbi Giuseppe (Italy), Kemlink David (Czech Republic), Laan Laura (The Netherlands), Neville Brian (United Kingdom), Nevšímalová Soňa (Czech Republic), Ninan Miriam (United Kingdom), Oechsler Claudia, Panagiotakaki Eleni (France), Spiel Georg (Austria), Bassi Maria Teresa (Italy), Casari Giorgio (Italy), Crawley Francis (Belgium), Martinelli Boneschi Filippo (Italy), Nicole Sophie (France), Poncelin Dominique (France), Sange Guenter (Austria), Schyns Tsveta (Austria), van den Maagdenberg Arn (The Netherlands), Vavassori Rosaria (Italy), Zucca Claudio (Italy).

1090-3798/$ – see front matter
doi:10.1016/j.ejpn.2011.08.006

Neurotransmitter disorder
GLUT-1 deficiency

4 cases, different MRC enzyme deficiencies were demonstrated, ranging from mild-unspecific deficiencies to more profound and probably primary defects. Although we did not find specific metabolic markers in our series, some metabolic disorders such as pyruvate dehydrogenase deficiency, MELAS, cerebral glucose transporter defect and neurotransmitter deficiency can exhibit symptoms similar to those of AHC and need to be ruled out before a diagnosis of AHC can be established. Further studies including high-throughput diagnostic technologies seem necessary to elucidate the etiology of this severe and enigmatic disorder.

1. Introduction

Alternating hemiplegia of childhood (AHC) is a rare disorder of unknown cause that was first described by Verret and Steel in 1971.[1] The diagnosis of AHC is usually difficult to make due to the variability of symptoms at onset, there often occurring a misdiagnosis of epilepsy or cerebral palsy.

AHC is characterized by an early onset, before 18 months of age, of repeated episodes of hemiplegia involving right or left side of the body lasting from minutes to days or weeks; episodes of bilateral hemiplegia or quadriplegia starting either as generalization of a hemiplegic episode or bilateral from the start; other paroxysmal disturbances including tonic/dystonic attacks, eye movement abnormalities (nystagmus, strabismus) and/or autonomic phenomena, occurring during hemiplegic bouts or in isolation. Typically, symptoms disappear during sleep, with recurrence 10–20 min after awakening in long-lasting bouts. Between episodes, patients present cognitive impairment and movement disorders such as choreoathetosis, dystonia and ataxia,[2–7] with evidence of non-progressive course.[8] Epilepsy is often associated.[9] Clinical symptoms are not attributable to other congenital or acquired neurological disorders. The diagnosis of AHC is purely clinical, as no laboratory, neuroradiological or genetic markers are currently available.

The pathogenic mechanisms of AHC remain an enigma. AHC was initially considered as a hemiplegic migraine variant[10] but the associated paroxysmal and non-paroxysmal symptoms, as well as the cognitive impairment in AHC, rule out this hypothesis. A channelopathy was considered based on the positive clinical response to Flunarizine, a non-selective blocker of voltage-dependent Ca^{+2} and Na^{+} channel[11,12] but genetic studies have failed to find any abnormality in genes associated with familial hemiplegic migraine and episodic ataxia (*CACNA1A*, *ATP1A2* and *SLC1A3* genes) in typical cases of AHC.[13–15] An epileptic mechanism can be ruled out because of the absence of seizures at the early stages of the disease and the lack of either EEG abnormalities or response to antiepileptic drugs in the majority of cases. In addition, the possibility of a mitochondrial etiology has been also considered but no consistent data have yet to confirm this hypothesis.[16–18]

Our main objective was to analyze the results of specific metabolic studies performed in a series of 157 European patients who fulfilled diagnostic criteria of AHC. We also tried to find a common metabolic abnormality related to AHC.

2. Patients and methods

2.1. The ENRAH project

European Network for Research on Alternating Hemiplegia (ENRAH) is a non-profit organization which was founded in 2003 in Vienna, Austria. Details of this consortium are described elsewhere.[8]

A questionnaire was designed by the ENRAH group and validated by the treating child neurologists in order to collect general information, clinical data (paroxysmal events, non-paroxysmal features), laboratory, neuroradiological, neurophysiological, and genetic studies, response to treatments administered, and trigger events. All data were collected at specific ages (<2 years, 6 years, 12 years, 18 years, and >18 years).

Participating physicians from 9 European countries collected clinical data, with the informed consent of the patient legal representative, after approval from independent national ethics committees, in accordance with European and national legislation and regulations. Data were collected retrospectively for the period preceding the onset of the project, and prospectively following evolution of the patients between April 2005 and June 2007. Information was validated by the ENRAH Validation Committee (AA, GG, BN) and afterwards transferred in electronic form to the European Registry. This electronic database is available on a secure Internet site (HC Forum® Internet platform) and access to the registry is secured by the use of a smart card (an integrated circuit card requiring a password and card reader). These data are accessible only to project participants or other persons with a research interest, following approval by the Steering Committee of ENRAH.

2.2. Patient inclusion

A total of 157 AHC patients (87 females and 70 males) were included in this study. All of them fulfilled clinical diagnostic criteria for AHC (Table 1) and were validated by an experts' committee before being included in the ENRAH registry. Typical cases were considered when satisfying criteria 1, 2, 3 and 7. When age of onset was after 18 months or episodes of bilateral hemiplegia were absent but patient fulfill all the other AHC diagnostic criteria, we considered the patient as an atypical case. Patients were aged between 9 months and 52

Table 1 – Clinical diagnostic criteria for AHC.

1. Onset before 18 months of age
2. Repeated bouts of hemiplegia involving right and left side of the body in some attacks
3. Episodes of bilateral hemiplegia or quadriplegia starting either as generalization of a hemiplegic episode or bilateral from the start
4. Other paroxysmal disturbances including tonic/dystonic attacks, nystagmus, strabismus, dyspnoea and other autonomic phenomena occurring during hemiplegic bouts or in isolation
5. Immediate disappearance of all symptoms upon sleep, with probable recurrence of long-lasting bouts 10–20 min after awakening
6. Evidence of developmental delay, mental retardation, neurologic abnormalities, choreoathetosis and dystonia or ataxia
7. Not attributable to other disorders

(a) Typical cases fulfill criteria 1, 2, 3 and 7.

years (median age at diagnosis was 20 months). Two pairs of siblings, of which one pair were monozygotic female twins, were included. Most patients were of Caucasian origin. Panagiotakaki et al. reported the clinical data and long-term course of the European series of AHC patients.[8]

2.3. *Metabolic data collected*

We retrospectively reviewed the metabolic studies performed in a series of 157 patients affected by AHC, at various stages of the disorder.

We analyzed the following parameters. **In blood**: lactate, pyruvate, creatine kinase, ammonia, plasma amino acids, lysosomal enzymes, very long chain fatty acids, and isoelectric focusing of serum transferrin. **In urine**: organic acids, purine, pyrimidine, oligosaccharide, mucopolysaccharide. **In cerebrospinal fluid (CSF)**: glucose, proteins, cell biogenic amines, pterins, folate, lactate, and amino acids). And, **in muscle biopsy:** determination of the mitochondrial respiratory chain (MRC) enzyme activities (complexes I, II, III and IV).

3. Results

The number of subjects for follow-up periods and the subjects studied for each metabolic exam are detailed in Table 2.

No significant abnormalities were found in metabolic investigations in blood and urine in typical or atypical cases, at different ages. Lumbar puncture and CSF examination were performed in 106 patients and reported as normal in all of them. Abnormal levels of glucose in CSF or low ratio of CSF glucose/plasma glucose were not reported in our series. Neurotransmitters in CSF were performed in 26 patients and were normal in all of them. In one case, elevated lactate and pyruvate values in blood and CSF were observed, but no further studies in muscle biopsy to rule out a mitochondrial encephalopathy were performed.

In 29 patients, muscular biopsy was done and the MRC enzyme activities were analyzed in 19 of them. Unspecific abnormalities in MRC were found in three cases. In two of them, deficiency of MRC complexes I–IV was detected, but no other biochemical (such as elevated lactate and plasma alanine, and low carnitine) or pathological markers of mitochondrial disorders (trichromic stain) were found. Therefore, mutational analysis of mitochondrial DNA was not carried out

Table 2 – Number of subjects for follow-up periods and subjects studied for each metabolic exam.

Metabolic exam	0–2 years (*n*: 157)		2–6 years (n: 144)		6–12 years (*n*: 107)		12–18 years (*n*: 70)		> 18 years (*n*: 51)	
	Patients studied	ND/NA	Patients studied	ND/NA	Patients studied	ND/NA	Patients studied	ND/NA	Patients studied	ND/NA
Base screening	114	43	58	86	36	71	24	46	12	39
Blood lactate	100	56	29	115	10	97	11	59	4	47
Blood pyruvate	79	78	23	121	6	101	9	61	2	49
Creatine kinase	62	95	29	115	12	95	8	62	6	45
Blood ammonia	86	71	30	114	8	99	9	61	4	47
Lysosomal enzymes	15	142	4	140	3	104	1	69	2	49
Plasma amino acids	87	70	16	128	9	98	9	61	5	46
VLFA	22	135	6	138	2	105	1	69	1	50
Transferrin IEF	30	127	4	140	3	104	–	70	2	49
Urine organic acids	78	79	18	126	8	99	7	63	5	46
Urine purine, pyrimidine	17	140	4	140	2	105	2	68	1	50
Urine oligosaccharide	21	136	5	139	5	102	1	69	2	49
Urine mucopolysaccaride	21	136	6	138	5	102	2	68	2	49
CSF (standard)	73	84	22	122	6	101	3	67	2	49
CSF neurotrasmitters	15	142	6	138	2	105	3	67	–	51
CSF pyruvate	22	135	6	138	–	107	–	70	–	51
CSF lactate	43	114	10	134	1	106	3	67	–	51
CSF amino acids	21	136	7	137	1	106	2	68	–	51
Muscle Biopsy	12	145	9	135	4	103	3	67	1	50
Mitochondrial chain analysis	9	148	4	140	2	105	–	70	4	47
Skin Biopsy	7	150	4	140	2	105	2	68	–	51

ND/NA: not done/not available; VLFA: very long chain fatty acids; IEF: isoelectric focusing; CSF: cerebrospinal fluid.

since no evidence suggesting the utility of this diagnostic approach was obtained.

A more evident MRC dysfunction was detected in two cases. In one patient, who died at 2 years and 6 months, 60% deficiency of complex II, 59% complex III, 60% complex IV (COX) and 30% reduction of complex II in skin biopsy were demonstrated. In the second patient, an isolated deficiency of cytochrome c activity was detected. Molecular genetic studies of mtDNA are currently being performed.

Finally, 3 further patients were studied for MERRF mutations (myoclonic epilepsy associated with ragged red fibers) and 3 for MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke), with negative results.

4. Discussion

The underlying disease mechanism in AHC remains unknown. Some hypotheses have been proposed such as hemiplegic migraine variant,[10] epileptic disorder and channelopathy, but without conclusive results. Biochemical investigations have been consistently unhelpful.[7]

In our series, basic metabolic screening tests were performed on almost all patients before diagnosis, and the results were generally normal, as in previous studies.[19]

Some authors have reported abnormalities in the skeletal muscle at rest and after exercise consistent with mitochondrial dysfunction in patients with AHC using ^{31}P magnetic resonance spectroscopy (MRS).[17,18] However, primary abnormalities in muscle mitochondria and mitochondrial enzyme activity have only been found in a few patients from a large series in which the authors studied muscle and skin biopsy in 38 patients affected by AHC; only one case with complex III deficiency was well documented.[19] Kyriakides et al.[20] studied muscular biopsy and analyzed MRC in one case of AHC and did not find any abnormality. Mikati et al.[7] reported the results of muscle biopsy as being normal in two and abnormal in three. Two demonstrated an increase in lipid content, one a decrease, and the other an increase in MRC activity. The third patient had subsarcolemmal clusters of mitochondria, with a generalized increase in MRC activity.[7]

Our results, as those of previous studies that evaluated a mitochondrial etiology, have been inconclusive. In addition, mitochondrial abnormalities that we and other authors found have not been fully characterized, and it is not known whether they are primary or secondary to another underlying etiology or are drug-induced abnormalities. Secondary mitochondrial abnormalities have also been reported in other neurological diseases, suggesting that in the absence of other diagnostic criteria, intermediate results of MRC enzymes should be interpreted with caution and clinicians should be actively looking for other underlying diagnoses.[21]

Although we have not found any metabolic marker related to AHC in our series, some metabolic disorders such as pyruvate dehydrogenase deficiency, MELAS, and glucose transporter (GLUT-1) defect can exhibit similar paroxysmal events (tonic/dystonic attacks, abnormal eye movements, hemiplegia) and neurological symptoms (movement disorders, ataxia, seizures, cognitive impairment)[22–24] and these need to be ruled out before a diagnosis of AHC can be made. In our series of patients, MELAS mutations were studied in three patients and the results were negative.

No abnormalities in CSF glucose/plasma glucose ratio were reported in our series, although in most cases testing was not done. Recently, a mutation in *SLC2A1* gene which codifies GLUT-1 was demonstrated to be associated with AHC in a single case,[25] suggesting that biochemical and genetic investigations for the diagnosis of GLUT-1 deficiency might be advisable in some selected cases.

In most infants who present with AHC, abnormal eye movements are the most precocious symptom, preceding the development of other paroxysmal neurologic phenomena. Similar episodic oculomotor abnormalities to AHC have been described in neurotransmitter deficiencies such as aromatic amino acid decarboxylase deficiency[26] and sepiapterin reductase deficiency (inborn errors of biopterin synthesis)[27]; both defects are treatable. CSF studies are needed to exclude these disorders. In our series, neurotransmitters in CSF were studied in only 26 patients of 157 and the results were normal in all of them. Our study exhibits some limitations: the data were mainly collected retrospectively through questionnaires and medical record reviews, and biochemical investigations performed in patients varied from country to country and from center to center in the same country, as patients are not usually centralized in one reference hospital.

In conclusion, we could not demonstrate a metabolic disorder related to AHC. However, it is important to rule out treatable metabolic disorders that can mimic AHC when there is clinical suspicion of the disorder. Further research, including high-throughput diagnostic technologies, is needed to elucidate the etiology of this severe and enigmatic disorder.

Acknowledgements

Special thanks to the following doctors for providing access to their patient files:

SPAIN: Arrabal L, Blanco B, Calvo MJ, Eiris J, García-Peñas JJ, Mora MD, Narbona J, Roche C, Rufo M, Velázquez R, Sans A.

FRANCE: Aicardi J, Arbues A S, Bednarek N, Billette T, Bourgeois M, Chaigne D, Chaunu MP, Chiron C, Cournelle AM, De StMartin A, Desguerres I, DesPortes V, Dulac O, Dusser A, Echenne B, Evrard P, Goutières F, Lazaro L, Motte J, Moutard ML, Nassogne MC, Neau JP, Pedespan JM, Penniello Valette MJ, Perelman S, Ponsot G, Pouplard F, Quillerou D, Rivier F, Roelens P, Vallée L, Vanhulle C.

ITALY: Santucci M, Tedesi B, Pantaleoni C, Zucca C, Pelliccia A, Piccinelli, Cardona F, Manfredi M, Galeone D, Laverda A, Dalla Bernardina B, Gambardella A, Vigevano F, Cotrufo R, Antonelli C, Granata T, Perini A, Di Rosa G, Gaggero R, Veneselli E.

GERMANY, AUSTRIA: Altmann B, Brand J, Fischer M, Gildberg K, Hallman V, Hantschel P, Heidelmann M Holthausen H, Kippert, Korinthenberg R, Krägeloh-Mann I, Kutschke G, Lauffer H, Laun J, Niemann G, Niethammer A, Opp J, Porsch P, Reinhardt W.Schmitt B, Schulze F, Skirl G, Steinlin M, Sterken W Stizmann FC, Strehl H, Traue C, Weidner B.

UNITED KINGDOM: Philip S, Short D, Childs AM, Jayawanth S, Das K, Hanna M, Wimalaratna S, Coldwell S, Cottrell A, Webb D, Gale A, Damman D.

CZECH REPUBLIC: Havlova M, Tauberova A, Prihodova I, Kemlink D.

THE NETHERLANDS, BELGIUM: van Nieuwenhuizen O, Coo R, Stroink H, Renier WO, Coo R, De Coo IFM, Arts WF, Eekhof JAH.

Special thanks to **Mrs. Tsveta Schyns** for initiating and coordinating the *ENRAH for SMEs* project, to **Mrs Rosaria Vavassori** for the management of the registry, to the AHC **family associations** in France, Italy, Spain, Germany, UK, and The Netherlands, and to **the patients**, **and their families**, who participated in the Registry and supported the project.

This work was supported by grant LSSM-CT-2005-516513 *ENRAH for SMEs* of the European Commission Research Program FP6 from April 2005 to June 2007.

REFERENCES

1. Verret S, Steele JC. Alternating hemiplegia of childhood: a report of eight patients with complicated migraine beginning in infancy. *Pediatrics* 1971;**47**:675–80.
2. Aicardi J. Alternating hemiplegia of childhood. *Int Pediatr* 1987; **2**:115–9.
3. Krageloh I, Aicardi J. Alternating hemiplegia in infants: report of five cases. *Dev Med Child Neurol* 1980;**22**:784–91.
4. Aicardi J, Bourgeois M, Fusco L, et al. Alternating hemiplegia of childhood. An overview. In: Andermann F, Aicardi J, Vigevano F, editors. *Alternating hemiplegia of childhood*. New York: Raven Press; 1995. p. 207–12.
5. Sakuragawa N. Alternating hemiplegia in childhood: 23 cases in Japan. *Brain Dev* 1992;**14**:283–8.
6. Bourgeois M, Aicardi J, Goutières F. Alternating hemiplegia of childhood. *J Pediatr* 1993;**122**:673–9.
7. Mikati MA, Kramer U, Zupanc M, Shanahan R. Alternating hemiplegia of childhood: clinical manifestations and long term outcome. *Pediatr Neurol* 2000;**23**:134–41.
8. Panagiotakaki E, Gobbi G, Neville B, et al. Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults. *Brain* 2010;**133**: 3598–610.
9. Neville B, Ninan M. The treatment and management of alternating hemiplegia of childhood. *Dev Med Child Neurol* 2007;**49**:777–80.
10. Hosking GP, Cavanagh NPC, Wilson J. Alternating hemiplegia: complicated migraine in infancy. *Arch Dis Child* 1978;**53**: 656–9.
11. Casaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984;**2**:579.
12. Sasaki M, Sakuragawa N, Osawa M. Long-term effect of flunarizine on patients with alternating hemiplegia of childhood in Japan. *Brain Dev* 2001;**23**:303–5.
13. Kors EE, Vanmolkot KR, Haan J, et al. Alternating hemiplegia of childhood: no mutations in the second familial hemiplegic migraine gene ATP1A2. *Neuropediatrics* 2004;**35**:293–6.
14. Haan J, Kors EE, Terwindt GM, et al. Alternating hemiplegia of childhood: no mutations in the familial hemiplegic migraine CACNA1A gene. *Cephalalgia* 2000;**20**:696–700.
15. De Vries B, Haan J, Stam AH, et al. Alternating hemiplegia of childhood: no mutations in the glutamate transporter EAAT1. *Neuropediatrics* 2006;**37**:302–4.
16. Arnold DL, Silver K, Andermann F. Evidence for mitochondrial dysfunction in patients with alternating hemiplegia of childhood. *Ann Neurol* 1993;**33**:604–7.
17. Kemp GJ, Taylor DJ, Barnes PR, Wilson J, Rada GK. Skeletal muscle mitochondrial dysfunction in alternating hemiplegia of childhood. *Ann Neurol* 1995;**38**:681–4.
18. Bhatt A, DeRoos S, Chillag K. Alternating hemiplegia of childhood with mitochondrial dysfunction: response to coenzyme Q10. *Eur J Paediatr Neurol* 2007; **11**, Suppl. 1: 127–128, unpublished communication.
19. Sweney MT, Silver K, Gerard-Blanluet M, et al. Alternating hemiplegia of childhood: early characteristics and evolution of a neurodevelopmental syndrome. *Pediatrics* 2009;**123**: 534–41.
20. Kyriakides T, Drousiotou A. No structural or biochemical evidence for mitochondrial cytopathy in a case of alternating hemiplegia of childhood. *Ann Neurol* 1994;**36**:805–6.
21. Hui J, Kirby DM, Thorburn DR, Boneh A. Decreased activities of mitochondrial respiratory chain complexes in non-mitochondrial respiratory chain diseases. *Dev Med Child Neurol* 2006;**48**:132–6.
22. Head RA, Brown RM, Zolkipli Z, et al. Clinical and genetic spectrum of pyruvate dehydrogenase deficiency: dihydrolipoamiden acetyltransferase (E2) deficiency. *Ann Neurol* 2005;**58**:234–41.
23. Klepper J, Leiendecker B. GLUT1 deficiency syndrome: 2007 update. *Dev Med Child Neurol* 2007;**49**:707–16.
24. Pavlakis SG, Phillips PC, DiMauro S, De Vivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. *Ann Neurol* 1984;**16**:481–8.
25. Rotstein M, Doran J, Yang H, et al. GLUT-1 deficiency and alternating hemiplegia of childhood. *Neurology* 2009;**73**: 2042–4.
26. Pons R, Ford B, Chiriboga CA, et al. Aromatic L-amino acid decarboxylase deficiency: clinical features, treatment, and prognosis. *Neurology* 2004;**62**:1058–65.
27. Neville BG, Parascandalo R, Farrugia R, Felice A. Sepiapterin reductase deficiency: a congenital dopa-responsive motor and cognitive disorder. *Brain* 2005;**128**:2291–6.