



ELSEVIER

journal homepage: www.elsevier.com/locate/epilepsyres



Early development in Dravet syndrome; visual function impairment precedes cognitive decline

Daniela Chieffo^a, Daniela Ricci^a, Giovanni Baranello^b, Diego Martinelli^a, Chiara Veredice^a, Donatella Lettori^a, Domenica Battaglia^a, Charlotte Dravet^a, Eugenio Mercuri^a, Francesco Guzzetta^{a,*}

^a Catholic University, Child Neurology and Psychiatry, Rome, Italy

^b Istituto Besta, Child Neurology and Psychiatry, Milan, Italy

Received 1 September 2010; received in revised form 26 October 2010; accepted 31 October 2010

KEY WORDS

Dravet syndrome;
Early development;
Visual function

Summary Aim of the study was to describe prospectively the early neuropsychological evolution including the first pre-cognitive stages of the Severe Myoclonic Epilepsy in Infancy (SMEI) or Dravet syndrome. Five cases, four of whom since before a diagnostic evidence of the Dravet syndrome, were followed up. Full clinical assessment including developmental, visual function and behaviour assessments were serially performed. In four cases, a variable onset age of cognitive decline assessed with developmental scales was preceded some months before by an impairment of visual function; the remaining patient during all the course of follow-up till 51 months of age showed a normal development without visual impairment. A cognitive decline with variable onset was generally confirmed in Dravet syndrome. The previous early impairment of visual function seems to herald the cognitive decline and provides useful prognostic information; furthermore, it possibly suggests some clues for a better understanding of the mechanisms of cognitive deterioration in this syndrome.

© 2010 Elsevier B.V. All rights reserved.

Introduction

Several studies have reported clinical findings in children affected with Severe Myoclonic Epilepsy in Infancy (SMEI) or Dravet syndrome (Dravet et al., 2002; Caraballo and Fejerman, 2006; Marini et al., 2007), but only three have

described details of neurodevelopmental features (Wolff et al., 2006; Riva et al., 2009; Ragona et al., 2010). The first study including a relatively small series was only partially prospective and provided short longitudinal assessments with developmental scales in few patients. A variable neurodevelopment was reported concerning both the degree of impairment and the onset of the cognitive decline. Furthermore, there was a certain asymmetry of the neuropsychological results with particular involvement in some cases of the abilities concerning visual function (visuo-constructive and visuo-spatial deficits). Only two were the patients followed up by Riva et al. (2009) with serial Grif-

* Corresponding author. Tel.: +39 0639155340.
E-mail addresses: fguzzetta@rm.unicatt.it,
francesco.guzzetta@alice.it (F. Guzzetta).

fiths' assessment till over 6 years showing a general decline of all the subscales. The third one was a retrospective study concerning a more numerous sample; it reported only global results obtained with Griffiths' Scales, Wechsler or clinical observation according to the age and level of collaboration. In all the papers there was no specific information about the pre-cognitive stage of development, namely of visual function that is known to be impaired in other forms of early onset epileptic encephalopathies such West syndrome (Jambaqué et al., 1993; Guzzetta et al., 2002). Mechanisms underlying neurodevelopment impairment could possibly operate since before the cognitive decline becomes evident at the usual developmental scales.

The aim of the study is to report details of the neurodevelopmental assessment including visual function and behaviour in five cases with Dravet syndrome, performed since the first year of life. Four of the 5 cases were prospectively assessed with early and serial assessments in an attempt to identify the onset of visual and neurodevelopmental difficulties; the remaining case (case 4) was admitted to our Unit at 24 months and subsequently serially assessed, while previously he had been examined elsewhere.

Patients and methods

The children enrolled in the study had typical findings and clinical and EEG evolution consistent with a diagnosis of Severe Myoclonic Epilepsy in Infancy (SMEI). Epileptic features, in fact, included an onset during the first year of life of febrile and afebrile generalized or unilateral tonic-clonic seizures, later associated with polymorphic seizures (partial, myoclonic and atypical absences); seizures were protracted, sometimes up to epileptic convulsive or non-convulsive status. EEG abnormalities were aspecific with focal or multifocal paroxysmal activities; in one case photosensitivity was observed. Clinical picture was typical in two cases and borderline with especially a lack of myoclonic seizures in the other three (cases 1, 4 and 5) (Table 1), even though their young age does not allow a definitive diagnosis. Four of the 5 (cases 1–3 and 5) were selected among a cohort of infants with severe febrile seizures followed longitudinally for a possible emergence of Dravet syndrome. The remaining Dravet case (case 4) came to our observation at a later stage when clear clinical signs of typical SMEI were already present.

Longitudinal follow-up

Mean of follow-up duration was 33.8 months with a range between 24 and 42 months. All five cases underwent serial assessments including neurological examination, neurodevelopmental scales and assessment of visual function. Informed consent was obtained from each patient's family. Children were generally assessed every 6–8 months compatibly with the family compliance; in some cases (3 and 4), in fact, there was some larger interval but the earliest assessments (during the first year of life) were always present.

Neurodevelopmental outcome was assessed using the Griffiths' mental Scales (Griffiths, 1996) including 5 domains (locomotor, personal-social, hearing and language, eye and

hand coordination, and performance) that provide a general quotient (GQ).

Visual function

The assessment of visual function includes abilities subcortical in origin (fixation and following) and especially with involvement of central processing (acuity, ocular motricity, fixation shift). Acuity was assessed binocularly using the Teller acuity card procedure and age-specific normative data (Mohn et al., 1988; Van Hof-van Duin et al., 1992).

Binocular visual fields were assessed using kinetic perimetry, using age-specific normative data (Van Hof-van Duin and Mohn, 1986; Van Hof-van Duin et al., 1992). Fixation shift test assesses visual attention by evaluating eye movements in response to a peripheral target (alternating black and white stripes) in the lateral field, according to the technique described by Atkinson et al. (1988).

Stereopsis was assessed using the Lang (1983) Stereotest random dots of Jules using age-specific stimuli and normative data.

Ocular motility was assessed by testing fixation, pursuit, and visual attention, to look for delaying in maturation or abnormalities.

Attention over distance was tested evaluating the distance at which the infant is able to maintain attention on a coloured toy presented on the midline in front of the eyes and gradually moved further away. The distance at which fixation is lost is taken as measure of the attention over distance.

Behaviour assessment

In the assessments performed after 18 months, behaviour problems were scored with Achenbach Child Behaviour Checklist for ages 1.5–5 (CBCL/1.5–5) (Achenbach and Rescorla, 2000).

Cases

We present in Table 1 the main clinical data of the five cases with Dravet syndrome while neurodevelopmental results are shown in Tables 2 and 3.

Case 1 was first assessed at 6 months; she presented a developmental quotient above 100 that showed a definite decline since 24 months.

All the aspects of visual function assessed also had normal results at 6 months with the exception of fixation shift that was persistently abnormal throughout the assessments. Since eighteen months up to the outcome (30 months) there was a pervasive impairment of visual function, less severe in visual field and ocular motility.

The CBCL showed normal results in all assessments with the exceptions of the last observation (30 months) showing abnormal scores in withdrawn, sleep and attention problems.

Case 2 was first assessed at 10 months and had a Griffiths' global quotient (GQ) within normal limits throughout the assessments in the first 24 months but there was a progressive decline that was more obvious after 39 months.

Table 1 Anagraphic and clinical data.

	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Female	Male	Female	Female	Female
Family history		Epilepsy and febrile seizures	Epilepsy		
Age of seizure onset	4 months, following legal vaccinations	4 months	4 months	5 months, 16 days	3 months
First seizure type	Gener. clonic, febrile, slightly lasting 1 h	Hemiclonic, febrile, lasting 15 min	Secondarily gener., afebrile, lasting 30 min	Hemiclonic, afebrile, repeated, lasting 15 min	Focal seizure (head and eyes tonic deviation to the left) lasting 2–3 min
Age of admission	6 months	10 months	12 months	24 months	10 months
Clinical examination	Normal	Normal	Normal	Normal	Normal
EEG	Normal	Normal	Abnormal	Normal	Abnormal
MRI	Normal	Normal	Normal	Normal	Normal
Follow-up duration	Up to 30 months	Up to 45 months	Up to 39 months	Up to 51 months	Up to 51 months
Seizures	Febrile and afebrile, gener. or hemiclonic alternating, often in clusters, protracted, 3 hemiclonic status, 1 GTC status no myoclonic seizure, rare atypical absences and rare focal seizures	Febrile and afebrile, gener. or right hemiclonic, in clusters, sometimes protracted 2 GTC.status, rare myoclonic seizures, no atypical absences, rare focal seizures	Febrile and afebrile gener. or hemiclonic alternating, in clusters, protracted, 3 GTC status, myoclonic seizures (ILS), rare atypical absences, focal seizures	Febrile and afebrile, gener. or hemiclonic alternating, in clusters, protracted, no status no myoclonic seizures, atypical absences, focal seizures	Focal seizures, febrile and afebrile, right and left hemiclonic, protracted or in clusters, no status, no myoclonic seizures, atypical absences, obnubilated status
EEG	Isolated centro-temporal SW, posterior slow waves	Normal until 13 months, central, fronto-central and vertex transitory SW	Normal until 9 months, multifocal, mainly bilateral centro-temporal, S and SW, gen.SW, photosensitivity	Multifocal S and SW isolated or in bouffées, short gen.SW discharges, variable lateralized SW	Normal until 32 months, isolated SW and sporadic and diffuse SW discharges
AEDs	VPA, CLB, TPM	PB, VPA, TPM	PB, VPA, CLB	VPA, CLB	VPA, CLB, TPM, CBZ (weaned at 32 months)
Genetics	No <i>SCN1A</i> mutation	No <i>SCN1A</i> mutation	No <i>SCN1A</i> mutation	<i>SCN1A</i> truncating mutation	No <i>SCN1A</i> mutation

GTC, generalized tonic-clonic; ILS, intermittent light stimulation; S, spikes; SW, spike-waves; VPA, valproic acid, CLB: clobazam, TPM, topiramate, PB: phenobarbital.

Table 2 Serial visual assessments.

Age	Ocular motility	Attention over distance	Acuity	Visual fields	Fixation shift	Stereopsis
<i>Case 1</i>						
6 months	○	○	○	○*	●	
8 months	○	○	○	○*	●	
18 months	◐	●	●	◐	●	
24 months	◐	●	●	◐	●	
30 months	◐	●	●	◐	●	
<i>Case 2</i>						
10 months	○	○	○	○	○	
15 months	○	○	○	○	○	
24 months	○*	●	●	○	●	○
32 months	○*	●	●	●	●	●
39 months	○*	●	●	●	●	●
45 months	●	●	●	●	●	●
<i>Case 3</i>						
12 months	○*	●	●	○	●	
32 months	●	●	●	◐	●	
39 months	●	●	●	●	●	
<i>Case 4</i>						
9 months						
24 months						
30 months	●	●	●	○*	●	
51 months	●	●	●	●	●	
<i>Case 5</i>						
10 months	○	○	○	○	○	
24 months						
30 months	○	○	○	○	○	
36 months						
42 months	○	○	○	○	○	
51 months						

●, abnormal; ◐, asymmetric; ○*, borderline or immature; ○, normal.

Visual function was persistently normal until the age of 24 months when attention at distance, acuity and fixation shift had abnormal results. After 32 months all the aspects of visual function assessed were abnormal with the exception of ocular motility that became abnormal at outcome (45 months).

The CBCL showed normal results in all assessments until 32 months when attention problems appeared; later on, there was a progressive deterioration that involved several behaviour disorders (sleep disorders, withdrawn and emotional reactivity).

Case 3 was first observed at 12 months and had a normal developmental quotient at Griffiths' Scales that resulted at 32 months definitely and generally deteriorated.

At 14 months attention at distance, acuity and fixation shift were already abnormal, and since 32 months all the other aspects of visual function were abnormal. The CBCL showed abnormal results in all the domains.

Case 4 was first observed at 24 months when there was already evidence of a Dravet syndrome; results of developmental assessment performed elsewhere at a pre-clinical stage (9 months of age) were normal. In our assessments at 24 and 30 months GQ was in the normal range but with relatively lower scores (up to 37 points) on motor and eye-hand

scales. However, at 51 months a definite cognitive decline was observed.

Visual function was assessed at 30 and 51 months: only visual fields were not abnormal at 30 months.

No behavioural problems emerged at CBCL.

Case 5 neurodevelopment was first assessed at 10 months and presented normal values of Griffiths' scales that persisted during all the follow-up till the last control at 51 months. Similarly, visual assessments always gave normal results. No behavioural disorders were found in any CBCL serial evaluation.

Discussion

The aim of this study was to precise the onset of neurodevelopmental abnormalities in a small cohort of children with Dravet syndrome and to assess possible early abnormalities of visual function before the evidence of a cognitive decline and even before the clinical confirmation of the epileptic syndrome.

In previous studies (Dravet et al., 1992, 2002; Caraballo and Fejerman, 2006; Ragona et al., 2010) different degrees of mental retardation and behavioural disorders have been

Table 3 Serial developmental and behavioural assessments.

Age	Griffiths' Scales						GQ	CBCL						
	A	B	C	D	E	F		a	b	c	d	e	f	g
<i>Case 1</i>														
6 months	100	108	100	108	108		105							
8 months	108	96	104	125	117		110							
18 months	127	128	112	116	117		123	52	50	50	55	51	51	50
24 months	95	95	90	80	85		89	60	59	52	68	60	63	52
30 months	93	95	82	83	82		88	60	59	58	70	70	77	51
<i>Case 2</i>														
10 months	100	109	77	86	86		92							
15 months	109	121	106	125	118		116							
24 months	92	117	96	96	96		99	52	50	58	51	53	51	50
32 months	93	118	87	87	100		97	59	50	63	67	62	73	50
39 months	93	118	87	87	100	82	77	68	58	60	65	72	85	68
45 months	80	89	84	67	62	93	79	70	56	58	72	73	78	50
<i>Case 3</i>														
12 months	87	100	100	93	97		95							
32 months	47	55	59	61	87		62	80	72	82	82	70	82	84
39 months	38	44	49	50	71		51	80	75	82	82	72	85	70
<i>Case 4</i>														
9 months							Bayley DQ	110						
24 months	91	140	130	93	95		108	50	50	50	50	50	50	50
30 months	92	140	142	83	127		120	50	50	52	51	50	62	56
51 months	74	94	88	71	78	82	80	50	50	56	54	50	65	58
<i>Case 5</i>														
10 months	100	98	115	103	103		102							
24 months	97	94	125	100	81		87							
30 months	110	110	121	105	84		105	50	50	50	50	50	50	50
36 months	106	100	122	109	100		110	50	50	50	50	50	65	50
42 months	110	110	121	105	84		105	50	50	50	50	50	50	50
51 months	90	102	102	86	86		94	50	50	50	50	50	65	50

Griffiths' Scales A: locomotor; B: personal–social; C: hearing and language; D: eye and hand coordination; E: performance; F: practical reasoning; GQ: general quotient. CBCL a: emotionally reactive; b: anxious/depressed; c: somatic complaints; d: withdrawn; e: sleep problems; f: attention problems; g: aggressive behaviour (digits in bold italic are abnormal). Behavioural data in bold: abnormal results.

reported in children with Dravet syndrome with various onset and evolution (Ragona et al., 2010). Wolff et al. (2006) reported 4 cases assessed in infancy using Brunet-Lézine scales, suggesting early neurodevelopmental difficulties since the first year of life with a trend towards a cognitive decline that stabilized after 4 years. The authors also reported specific visuo-spatial and visuo-constructive difficulties: these could be a sign of age-related brain dysfunction, with a specific parieto-occipital location, similar to that observed in West syndrome (Jambaqué et al., 1993). A progressive decline since the second year of life irrespectively to the different course of their epileptic histories was found by Riva et al. (2009) in two cases. Definite cognitive impairment was also reported by Caraballo and Fejerman (2006) "since 2 years of age". Only in one anecdotic case with a novel SCN1A (2528delG) truncating mutation a normal clinical and developmental outcome (at 13 years) was observed (Buoni et al., 2006).

In our study we were able to obtain early and serial assessments in four of our five patients with Dravet syndrome, clinically typical in two and borderline in three,

according to the criteria described by Dravet et al. (1992); they were followed at least till 30 months (case 1) and even over 4 years of age (cases 4 and 5). In one of our patient (case 2) a definite cognitive decline appeared at a later age (39 months) than generally reported in the literature. In another case (case 3) the documented decline was found also at later age (32 months) but the previous assessment at 14 months was too early to allow the settlement of the decline onset as late. However, a cognitive decline even though in a borderline range occurred at 24 months in case 1. In case four followed by our Unit only since he was 24 months old, GQ value that were still optimal at 30 months fell at 51 months. It is worthy noting a generally present asymmetry of subscale results in cognitive decline especially concerning eye–hand coordination abilities; it was consistent with visuo-spatial and visuo-constructive difficulties reported by Wolff et al. (2006) and with the concurrent impairment of the visual function in our cases. Totally different was the cognitive development in case 5; since the age of 10 months up to more than four years global quotient remained stable in the normal range.

We were also able to perform a detailed assessment of various aspects of visual function, showing that four children, when assessed in the second year or in the first half of the third year (case 4), have a diffuse involvement of most, if not all the aspects of visual function explored; visual fields and ocular motility apparently seems attained more later than the other measured skills.

In these four cases the abnormalities of visual function were obvious before those of the neurodevelopmental scale, in some way heralding the beginning of the neurocognitive involvement. The predictive value of impaired visual function versus cognitive development has been previously shown in early brain injured (Mercuri et al., 1999) or epileptic infants with West syndrome (Guzzetta et al., 2008). Nonetheless, in West syndrome pre-cognitive (early visual function) and cognitive impairment seem to occur earlier than in Dravet syndrome; yet, the sequential occurrence of sensory and cognitive impairments could suggest a possible down-top modality of the causal relationship between visual involvement and subsequent cognitive decline. The later onset of visual impairment in Dravet syndrome when cognitive development is already established could account for a developmental delay that rarely shapes the early and catastrophic profile of the West syndrome.

It is also noteworthy that behavioural problems appeared later than the other developmental abnormalities, possibly suggesting a secondary phenomenon related to cognitive deterioration; in the fourth case, however, behavioural disorders were not yet present even at the last observation (51 months).

As to the cause of the early visual function impairment before the manifestation of severe seizures, it should be evoked a role of factors other than epilepsy activity (seizures and electrical abnormalities). It is worthy underlining that, even though it was found only in one case of ours, the genetic mutation (SCN1A) with a loss of function in Nav1.1 (a voltage-gated sodium channel lacking in SMEI) often observed in Dravet syndrome is expected from experimental studies to determine a decreased excitability of cerebellar Purkinje neurons (Kalume et al., 2007); this dysfunction may extend its effects on the visual function, namely on the visuo-motor control (Cerminara et al., 2009). On the other hand, the same cerebellar dysfunction deriving from the sodium channel impairment may play a role in determining a general developmental delay (Schmahmann, 2004).

An atypical course of development was observed in case 5 that showed neither visual impairment nor cognitive decline. In the wide array of development phenotypes, only another case of Dravet syndrome in literature (Buoni et al., 2006) showed at 13 years normal cognitive abilities. In this case authors stressed that the lack of cognitive decline could be explained by the seizure reduction after 4 years. In our case no particular epileptic evolution was found; it is noteworthy to underline that visual function development in our case 5 was normal since the first assessments, in some way predicting the normal cognitive development.

The number of our series is too small and the timing of the assessments too scattered to allow to draw any definite conclusions or to attempt meaningful correlations with the evolution of seizures and with treatment or with the genetic background, whose phenotypic variability is stressed

by recent papers (Ohmori et al., 2003; Marini et al., 2007). Nevertheless our preliminary data suggest that early and sequential assessments of visual function should be performed as early as possible. The presence of an impairment of the visual function preceding the cognitive decline could in fact provide useful prognostic information, besides some clues for a better understanding of the mechanisms of cognitive deterioration in this syndrome. Moreover, the evidence of a sensory deterioration before the seizure manifestations would account for a multifactorial genesis of developmental decline with some factor other than epilepsy.

Our observations confirm and widen the large array of neuropsychological phenotypes in Dravet syndrome. Variable onset of the disease is confirmed in our patients who demonstrated that subclinic sensory disorders indicating earlier deteriorations may occur before the clear manifestation of the syndrome. It has also been observed in this small sample a case of normal development, a finding that could be underestimated in a generally *a posteriori* evaluation of the patients with Dravet syndrome. We think thus that accurate prospective assessments of neuropsychological development may contribute to the definition of Dravet syndrome with their phenotype–genotype correlations.

Further prospective developmental studies with longer follow-up in a larger cohort of patients could give a better insight about the definition of Dravet syndrome and mechanisms underlining its clinical findings.

Acknowledgements

We warmly thank Mariani Foundation for supporting Dr. Daniela Chieffo in this study (Mariani Foundation, Viale Bianca Maria 28, 20129 Milano. Tel.: +39 02795458; fax: +39 0276009582. E-mail: info@fondazione-mariani.org). The remaining Authors have no conflicts of interest.

References

- Achenbach, T.M., Rescorla, L.A., 2000. Manual for the ASEBA Preschool Forms and Profiles. University of Vermont, Department of Psychiatry, Burlington, VT.
- Atkinson, J., Hood, B., Braddick, O.J., Wattam-Bell, J., 1988. Infants' control of fixation shifts with single and competing targets: mechanisms of shifting attention. *Perception* 17, 367–368.
- Buoni, S., Orrico, A., Galli, I., Zannoli, R., Burrioni, L., Hayek, J., Fois, A., Sorrentino, V., 2006. SCN1A (2528delG) novel truncating mutation with benign outcome of severe myoclonic epilepsy of infancy. *Neurology* 66, 606.
- Caraballo, R.H., Fejerman, N., 2006. Dravet syndrome: a study of 53 patients. *Epilepsy Res.* 70S, S231–S238.
- Cerminara, N.L., Apps, R., Marple-Horvat, D.E., 2009. An internal model of a moving visual target in the lateral cerebellum. *J. Physiol.* 587 (Pt 2), 429–442.
- Dravet, C., Bureau, M., Roger, J., 1992. Severe myoclonic epilepsy. In: Roger, J., Bureau, M., Dravet, C., Dreifuss, F.E., Perret, A., Wolf, P. (Eds.), *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 2nd ed. John Libbey, London, pp. 75–88.
- Dravet, C., Bureau, M., Oguni, H., Fukuyama, Y., Cokar, O., 2002. Severe myoclonic epilepsy in infancy (Dravet syndrome). In: Roger, J., Bureau, M., Dravet, C., Genton, P., Tassinari, C.A., Wolf, P. (Eds.), *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 3rd ed. John Libbey, London/Paris, pp. 81–103.

- Griffiths, R., 1996. The Abilities of Young Children. The Test Agency, High Wycombe, UK.
- Guzzetta, F., Frisone, M.F., Ricci, D., Randò, T., Guzzetta, A., 2002. Development of visual attention in West syndrome. *Epilepsia* 43, 757–763.
- Guzzetta, F., Cioni, G., Mercuri, E., Fazzi, E., Biagioni, E., Veggiotti, P., Bancale, A., Baranello, G., Epifanio, R., Frisone, M.F., Guzzetta, A., La Torre, G., Mannocci, A., Randò, T., Ricci, D., Signorini, S., Tinelli, F., 2008. Neurodevelopmental evolution of West syndrome: a 2-year prospective study. *Eur. J. Paediatr. Neurol.* 12, 387–397.
- Jambaqué, I., Chiron, C., Dulac, O., Raynaud, C., Syrota, P., 1993. Visual inattention in West syndrome: a neuropsychological and neurofunctional imaging study. *Epilepsia* 34, 692–700.
- Kalume, F., Yu, F.H., Westenbroek, R.E., Scheuer, T., Catterall, W.A., 2007. Reduced sodium current in Purkinje neurons from Nav1.1 mutant mice: implications for ataxia in severe myoclonic epilepsy in infancy. *J. Neurosci.* 27, 11065–11074.
- Lang, J., 1983. A new stereotest. *J. Pediatr. Ophthalmol. Strabismus* 20, 72–74.
- Marini, C., Mei, D., Temudo, T., Ferrari, A.R., Buti, D., Dravet, C., Dias, A.I., Moreira, A., Calado, E., Seri, S., Neville, B., Narbona, J., Reid, E., Michelucci, R., Sicca, F., Cross, H.J., Guerrini, R., 2007. Idiopathic epilepsies with seizures precipitated by fever and *SCN1A* abnormalities. *Epilepsia* 48, 1678–1685.
- Mercuri, E., Haataja, L., Guzzetta, A., Anker, S., Cowan, F., Rutherford, M., Andrew, R., Braddick, O., Cioni, G., Dubowitz, L., Atkinson, J., 1999. Visual function in term infants with hypoxic-ischemic insults; correlation with neurodevelopment at 2 years of age. *Arch. Dis. Child Fetal Neonatal.* Ed. 80, F99–F104.
- Mohn, G., van Hof-van Duin, J., Fetter, W.P., de Groot, L., Hage, M., 1988. Acuity assessment of nonverbal infants and children: clinical experience with the acuity card procedure. *Dev. Med. Child Neurol.* 30, 232–244.
- Ohmori, I., Ohtsuka, Y., Ouchida, M., Ogino, T., Maniwa, S., Shimizu, K., Oka, E., 2003. Is phenotype difference in severe myoclonic epilepsy in infancy related to *SCN1A* mutations? *Brain Dev.* 2–5, 488–493.
- Ragona, F., Brazzo, D., De Giorgi, I., Morbi, M., Freri, E., Teutonico, F., Gennaro, E., Zara, F., Binelli, S., Veggiotti, P., Granata, T., 2010. Dravet syndrome: early clinical manifestations and cognitive outcome in 37 Italian patients. *Brain Dev.* 32, 71–77.
- Riva, D., Vago, C., Pantaleoni, C., Bulgheroni, S., Mantegazza, M., Franceschetti, S., 2009. Progressive neurocognitive decline in two children with Dravet syndrome, de novo *SCN1A* truncations and different epileptic phenotypes. *Am. J. Med. Genet. A* 149A, 2339–2345.
- Schmahmann, J.D., 2004. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J. Neuropsychiatry Clin. Neurosci.* 16, 367–378.
- Van Hof-van Duin, J., Mohn, G., 1986. The development of visual acuity in normal fullterm and preterm infants. *Vision Res.* 26, 909–916.
- Van Hof-van Duin, J., Heersema, D.J., Groenendaal, F., Baerts, W., Fetter, W.P., 1992. Visual field and grating acuity development in low-risk preterm infants during the first 2 1/2 years after term. *Behav. Brain Res.* 49, 115–122.
- Wolff, M., Cassé-Perrot, C., Dravet, C., 2006. Severe myoclonic epilepsy of infants (Dravet Syndrome): natural history and neuropsychological findings. *Epilepsia* 47 (Suppl. 2), 45–48.