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Progressive demyelinating neuropathy correlates with clinical severity in Cockayne syndrome

Cyril Gitiaux [a,b,*], Nathalie Blin-Rochemaure [c], Marie Hully [a], Andoni Echaniz-Laguna [d], Nadège Calmels [e], Nadia Bahi-Buisson [a], Isabelle Desguerre [a], Ivana Dabaj [c], Samer Wehbi [f], Susana Quijano-Roy [c], Vincent Laugel [g]

[a] Service de Neurologie Pédiatrique et Maladies Métaboliques, Hôpital Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
[b] Service d'explorations Fonctionnelles, Laboratoire de Neurophysiologie Clinique, Hôpital Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
[c] Service de Pédiatrie, Hôpital de Garches, Garches, France
[d] Département de Neurologie, CHU Hautepierre, F-67098 Strasbourg, France
[e] Laboratoire de Diagnostic Génétique, Nouvel Hôpital Civil, F-67091 Strasbourg, France
[f] Service de Pédiatrie, Hôpital de Versailles, Versailles, France
[g] Laboratoire de Génétique Médicale, INSERM 1112, Faculté de Médecine, F-67085 Strasbourg, France

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HIGHLIGHTS

- Nerve conduction studies are helpful in guiding the diagnosis of Cockayne syndrome (CS) but normal findings may be observed in the first months of life.
- Conduction velocity is negatively correlated to the clinical severity (CS subtypes).
- Data suggest a progressive course of the neuropathy within the first year, which may be relevant if therapeutic trials are intended.

ABSTRACT

Objective: Cockayne syndrome (CS) is characterized by postnatal growth failure and progressive multi-organ dysfunctions. CSA and CSB gene mutations account for the majority of cases and three degrees of severity are delineated. A peripheral neuropathy is known to be associated with CS but the type, severity and correlation of the nerve involvement with CS subtypes remain unknown in genetically identified patients.
Methods: Clinical and nerve conduction studies (NCS) in 25 CS patients with CSA ($n = 13$) CSB ($n = 12$) mutations.
Results: NCS show a widespread decrease in motor and sensory conduction velocities (CV) in all severe and classical form of CS. In one patient, CV were normal at age 8 months but severe slowing was detected at 2 years. Conduction block and/or temporal dispersion were observed in 68% of patients.
Conclusions: CS is associated with a progressive sensory and motor neuropathy. Signs of segmental demyelination, including conduction blocks, may not be obvious before the age of 2 years. CV slowing is correlated with the CS clinical severity.
Significance: NCS should be performed in patients with suspected CS as an additional tool to guide the diagnosis before molecular studies. Further studies focused on NCS course are required in order to assess its relevance as a biomarker in research therapy projects.

1. Introduction

Cockayne syndrome (CS) is an autosomal recessive disorder predominantly characterized by progressive neurological and cognitive dysfunction, microcephaly, severe growth failure,

* Corresponding author at: Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75015 Paris, France. Fax: +33 1 42 19 26 92.
E-mail address: cyril.gitiaux@nck.aphp.fr (C. Gitiaux).

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sensorial impairment, cutaneous photosensitivity, dental decay, and specific facial appearance with deep sunken eyes. The minimal incidence of CS has been evaluated in Western Europe at 2.7 cases per million births (Kleijer et al., 2008). A diagnostic feature of CS is the impaired recovery of RNA synthesis in fibroblasts of patients after UV irradiation (Mayne and Lehmann, 1982). This condition is related to defective DNA transcription and/or repair and belongs to the family of DNA nucleotide excision repair (NER) disorders together with xeroderma pigmentosum (XP) and trichothiodystrophy (TTD) (Kleijer et al., 2008; Laugel, 2013). The clinical spectrum of CS encompasses a wide range of severity. Patients have been divided into subgroups based on age at disease onset as well as on symptom severity: type II patients are characterized by the presentation of canonical symptoms from birth and by a short life span (2–7 years), type I patients display most symptoms in their first 2 years of life and have a mean life expectancy of 16 years, and type III patients show a later onset of the disease and have a prolonged survival until adulthood (Nance and Berry, 1992; Laugel et al., 2010; Laugel, 2013). The very severe cerebro-oculo-facio-skeletal (COFS) syndrome involves the same cellular defect as CS and can be regarded as a prenatal form of CS with a very poor prognosis (Laugel et al., 2008). Two major genes are responsible for the disorder, ERCC6 (CSB) and ERCC8 (CSA) (Troelstra et al., 1992; Henning et al., 1995). Even though no clear genotype/phenotype correlation exists (Newman et al., 2008; Laugel et al., 2010; Bailey et al., 2012). An expanding spectrum has been described which confirms the huge clinical variability of CS, suggesting that it is still likely to be substantially underdiagnosed. Therefore, reliable criteria for diagnosis remain important to identify. Little is known about the peripheral involvement in CS and the relation between clinical features, neurophysiological and molecular data. Peripheral nerve involvement is usually described as a demyelinating neuropathy but most case reports were published before the identification of the genes responsible for the disease (Moosa and Dubowitz, 1970; Vos et al., 1983; Nance and Berry, 1992; Özdirim et al., 1996). Its frequency, severity and correlation with CS subtypes remain ill-defined. Hence, in order to refine the description of clinical involvement in CS, we conducted a retrospective evaluation of electroneuromyographic (ENMG) findings in a series of 25 genetically confirmed CS patients who underwent neurophysiological investigations tests for the presence of peripheral neuropathy. Furthermore, we analyzed the correlations between neurophysiological, clinical, and molecular data.

2. Patients and methods

2.1. Patients

Twenty-five patients (16 male/9 female) with documented CSA or CSB mutations consistent with a genetic diagnosis of Cockayne syndrome, were identified at the French reference center and underwent the investigations described in detail below. Each patient was further categorized according the classical diagnostic criteria (COFS: arthrogryposis, congenital microcephaly, congenital cataracts and/or microphthalmia, severe developmental delay, severe post natal failure; CS type II (CS-II): early onset or severe subtype; CS type I (CS-I): classical or moderate subtype; CS type III (CS-III): late onset or mild subtype) (Nance and Berry, 1992; Laugel, 2013). Informed parental consent was obtained prior to the diagnostic procedures.

2.2. Methods

2.2.1. Nerve conductions studies

ENMG evaluations were performed either in the context of progressive encephalopathy associated with clinical signs of peripheral neuropathy or after the genetic diagnosis. These ENMG studies were reviewed retrospectively. All electrophysiological testing was performed by an expert pediatric neurologist experienced in pediatric ENMG studies (AEL-CG-SQR) using a Medtronic Keypoint device (Alpine Biomed, USA). Before nerve conduction studies (NCS) were performed, the temperature was checked, and cool limbs (<32 °C) were warmed. For motor NCS, each electrodiagnostic examination included at least one peroneal, and/or one posterior tibial nerve. Motor NCS were also recorded in fifteen cases in at least one median nerve. Distal latency (DL), peak to baseline amplitude of the compound muscle action potentials (CMAPs), motor nerve conduction velocity (MNCV) and F-wave latency (F-WL) were recorded using standard procedures. CMAPs were evaluated for abnormal temporal dispersion (defined as an increase of $\geqslant$30% in CMAP duration on proximal compared with distal stimulation) or conduction block (decrease of $\geqslant$50% of CMAP amplitude on proximal compared with distal stimulation). For sensory NCS, each examination included at least one sural nerve. Occasionally, sensory NCS were also recorded in median nerves. Sensory NCSs were performed antidromically in the lower limb and orthodromically in the upper limb routinely. Distal latency (DL), baseline to peak amplitude of the sensory nerve action potential (SNAP) and sensory nerve conduction velocity (SNCV) were measured. Raw data of sensory and motor NCS were analyzed to age matched reference values and expressed as a percentage of decrease/increase compared to normal values for age (Normal references values are provided in the Supplementary Table S1) (Bolton and Royden Jones, 1995).

2.3. Statistical method

Data are presented as mean ± SEM. Comparisons between groups were performed using *t* test. Spearman's rank correlation coefficient was used to assess correlation between CS subtypes of severity and nerve conductions velocities. *p* values less than 0.05 were considered statistically significant. All statistical analyses were conducted using R software version 3.00.

3. Results

4.1. Clinical data

The diagnosis of CS was confirmed in all patients: 13 patients display mutations in the CSA (ERCC8) gene and 12 patients in the CSB (ERCC6) gene. 7, 15 and 3 patients were classified as COFS/CS-II, CS-I, and CS-III respectively. Most patients show a combination of pyramidal extrapyramidal and cerebellar signs. Peripheral involvement was often not clinically obvious except for diminished or absent deep tendon reflexes. The main clinical and genetic data are provided in Table 1.

4.2. Characterization of peripheral nerve involvement

Detailed NCS findings are presented in Table 2. In all 25 cases but predominantly for the severe and classical types of CS, an electrophysiological pattern suggestive of primary sensory and motor demyelinating neuropathy was observed. Indeed, the main neurophysiological finding was a widespread decrease in motor nerve conduction velocities (MNCV), in the upper (UL) and lower limbs (LL), reflecting a demyelinating pattern (median: −37.2%; tibial: −41.5%; peroneal: −44.2%; mean% of decrease compared to normal values). Block of conduction or abnormal temporal dispersion identified on peroneal or median nerves were frequent (17/25) (Fig. 1). F-waves when recorded were always altered mainly at the UP (median: +69%; tibial: +43.5% F-WL; mean% of increase compared