Doc Ophthalmol (2019) 138:241–246
https://doi.org/10.1007/s10633-019-09681-y

CLINICAL CASE REPORT

Cockayne syndrome in adults: complete retinal dysfunction exploration of two case reports

Marc Figueras-Roca · Vanessa Budi · Montserrat Morató · Anna Camós-Carreras · José Esteban Muñoz · Bernardo Sánchez-Dalmau

Received: 23 December 2018 / Accepted: 19 February 2019 / Published online: 28 February 2019

Abstract
Purpose Cockayne syndrome is a rare autosomal recessive disease, also known as a *progeria* disorder, causing dwarfism, senile appearance and multiple systemic affections. Ophthalmic abnormalities are frequent, for example, in the forms of pigmentary retinopathy with low visual acuity. We present two genetic-confirmed cases with a detailed electrophysiological exploration of their retinal findings.
Methods Complete ophthalmic exploration is undertaken, including full-field electroretinogram under ISCEV guidelines and multifocal electroretinogram (RETI-scan science, Roland-Consult, Germany), ultra-wide-field retinography and autofluorescence (Optomap, Optos PLC, Dunfermline, Scotland, UK) and macular and retinal nerve fibre layer optical coherence tomography (Cirrus, Carl-Zeiss Meditec, Inc, Dublin, CA).
Results Both cases presented with CSA/ERCC8 mutation and low visual acuity. Diffuse pigmentary retinopathy with macular atrophy was found in ultra-wide-field retinography and autofluorescence. Electrophysiological testing reported wide retinal dysfunction on both cone and rod system with macular involvement.
Conclusions Pigmentary retinopathy in CS could translate a wide dysfunction of the retina with major affection of external retinal layers of both cone and rod cells. Macular implication is also present and could explain progressive vision loss in such cases.

Keywords Cockayne syndrome · Progeria · Electroretinogram · Pigmentary retinopathy

M. Figueras-Roca (✉) · V. Budi · M. Morató · A. Camós-Carreras · B. Sánchez-Dalmau
Institut Clínic d'Oftalmologia (ICOF), Hospital Clínic, Sabino de Arana St. (Casa Maternidad, 2nd floor), 08028 Barcelona, Spain
e-mail: mafiguer@clinic.cat

M. Figueras-Roca · A. Camós-Carreras · J. E. Muñoz · B. Sánchez-Dalmau
August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain

J. E. Muñoz
Department of Neurology, Hospital Clínic, Barcelona, Spain

Introduction

Cockayne syndrome (CS) is a rare condition characterized by cachectic dwarfism and progressive neurological dysfunction. Additional features include microcephaly, cognitive and motor defects, skin photosensitivity, senile appearance, pigmentary retinopathy, cataracts and deafness [1, 2]. CS behaves as an autosomal recessive disorder with an estimated prevalence of 2.5 per million. It results from mutations in the CSB/ERCC6 or CSA/ERCC8 genes, which are

involved in repairing damaged DNA and assisting with gene transcription [1–3]. CS is considered a *progeria* able to present with different phenotypes but usually causing death during the two first decades of life. However, type 3 CS characteristically presents with a milder form with longer life expectancy. Pigmentary retinopathy is the most frequent ocular finding (60–100%) and has been reported to show abnormal electroretinogram recordings even before clinical impairment is recognized [1, 4]. We present two cases of adult CS that undertook a complete eye electrophysiological exploration, including full-field electroretinogram and multifocal electroretinogram, together with the latest cutting-edge retinal imaging techniques as ultra-wide-field retinography and autofluorescence.

Case report

Two siblings, a 44-year-old male (case A) and a 41-year-old female (case B), presented with typical clinical features including dwarfism, senile appearance, microcephaly and progressive neurological dysfunction. CS was genetically confirmed by CSA/ERCC8 gene exon 5 homozygous mutation (c. 478 G > A (Ala160Thr)) as had been previously published [2]. Best achieved visual acuity in case A was 20/60 right eye and 20/200 left eye, while case B presented with 20/400 in both eyes. Progressive visual acuity loss was documented by past medical history recording it to be 20/40 in both eyes (case A) and 20/50 in both eyes (case B) 6 years ago. No significant abnormalities were noted in the anterior segment. Funduscopy under pupil dilation showed optical disc pallor, arteriole narrowing and retinal pigment epithelium (RPE) mottling with diffuse pigment clumping. Ultra-wide-field retinography and autofluorescence (Optomap, Optos PLC, Dunfermline, Scotland, UK) were performed proving extensive RPE changes (Fig. 1). Spectral-domain optical coherence tomography (OCT) (Cirrus, Carl-Zeiss Meditec, Inc, Dublin, CA) showed foveal atrophy with disruption of external retinal structures (Fig. 2) such as the RPE/Bruch's complex band, outer segments of the photoreceptor layer and ellipsoid zone. OCT built-in manufacturer software determined a lessened mean retinal nerve fibre layer thickness in both cases (77 μm in case A right eye, 57 μm in case A left eye, 60 μm in case B right eye and 58 μm in case B left eye) together with a

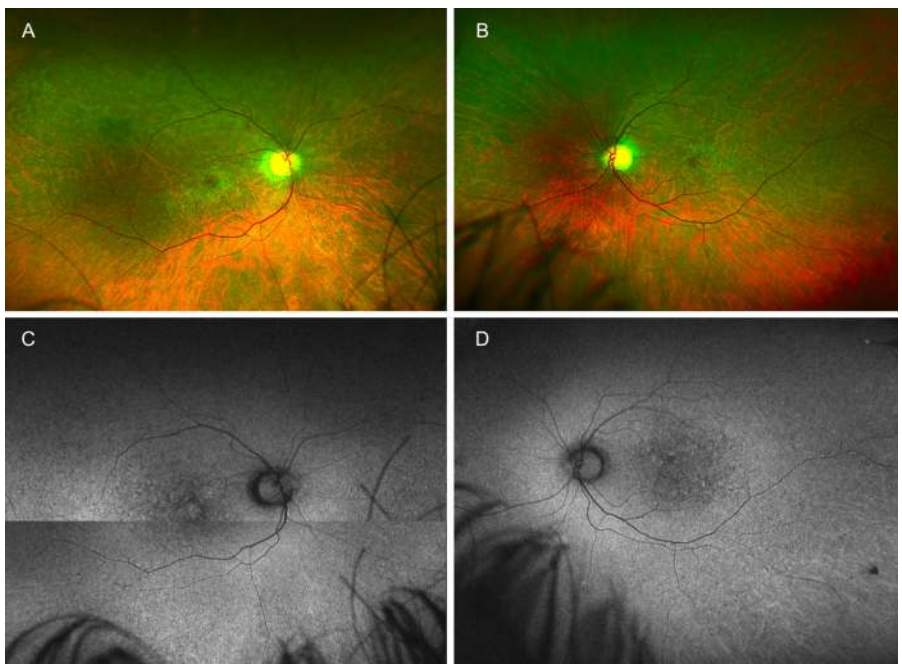

Fig. 1 Ultra-wide-field retinography of right eye (**A**) and left eye (**B**) in case B. Same subject's ultra-wide-field autofluorescence of right eye in composition (**C**) and left eye (**D**)

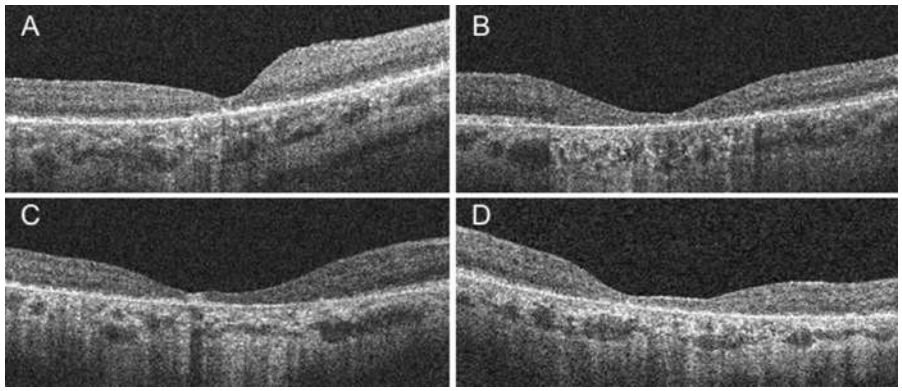

Fig. 2 Optical coherence tomography of the foveal area of the macula of right eye (**A**) and left eye (**B**) of case A and right eye (**C**) and left eye (**D**) of case B

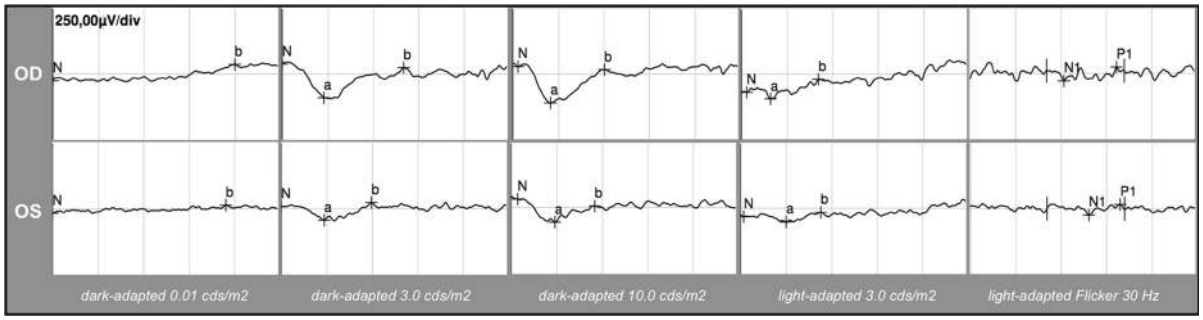

Fig. 3 Full-field electroretinogram of right eye (OD) and left eye (OS) of case A

diffuse decrease in ganglion cell layer thickness in both eyes of the siblings. Eye electrophysiological testing (RETI-scan science, Roland-Consult, Germany) by full-field flash electroretinogram (FF-ERG) and multifocal electroretinogram (MF-ERG) was undertaken according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards [5, 6]. Regarding FF-ERG (Figs. 3, 4), dark-adapted 0.01 cds/m^2 stimulus presented with a complete absence of response on left eye of case A and right eye of case B, with the other eyes showing a diminished response. Dark-adapted 3.0 cds/m^2 and 10.0 cds/m^2 stimulus reported a lessened *a wave* with a reduced *b wave* resulting in a lower *b* to *a* ratio in an electronegative form. Moreover, both cases showed a complete abolition of signal on light adapted 3.0 cds/m^2 and 30 Hz flicker. MF-ERG (Fig. 5) reported disrupted and decreased signals in central and paracentral rings of both eyes of case A with greater alteration of peripheral areas; on the other hand, case B showed a wide abolition of signal in both eyes.

Discussion

CS is considered a *progeria* disease directly related to abnormal repairing of damaged DNA and gene transcription because of dysfunctional CSB/ERCC6 or CSA/ERCC8 genes [1, 2]. Among many other clinical findings, retinal dystrophy is one of the most frequent and seems to be related to direct cell affection. However, little has been reported in relation to the functional exploration of such retinal dysfunction, with some authors claiming severe alterations whereas others finding none [1, 7]. Our CS presented cases are characteristically old for the presumed life expectancy of this disease, and therefore, the results of their exploration could be considered of great importance for an overall timely understanding of CS retinal changes.

Ultra-wide-field retinography and autofluorescence as well as OCT findings are consistent to recently reported cases [8], showing diffuse pigmentary retinopathy, also affecting the macular area, with

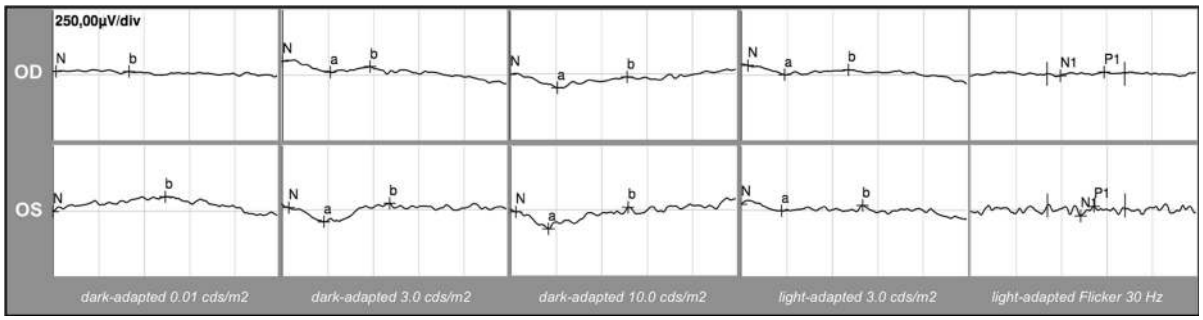

Fig. 4 Full-field electroretinogram of right eye (OD) and left eye (OS) of case B

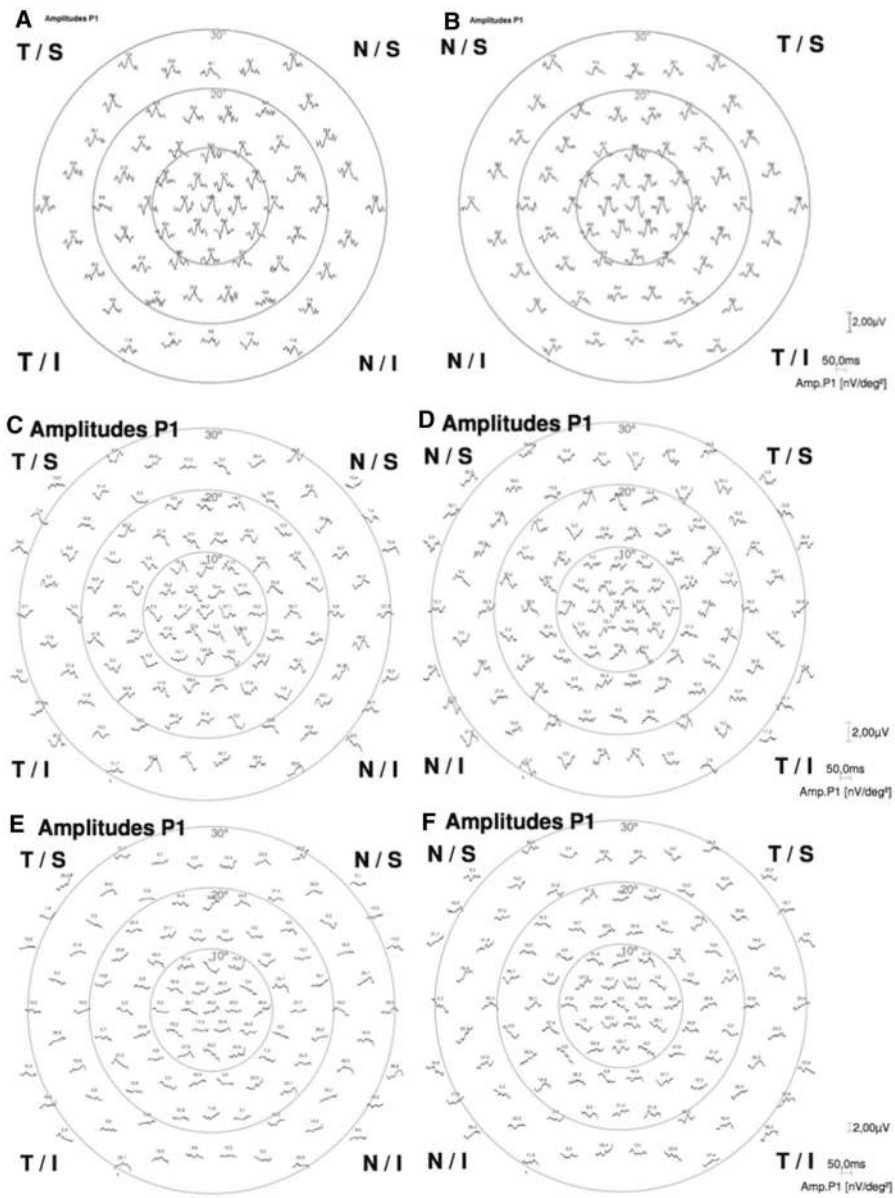

Fig. 5 Multifocal electroretinogram of a non-pathologic example right eye (**A**) and left eye (**B**) and presented Cockayne syndrome case reports: case A right eye (**C**), case A left eye (**D**), case B right eye (**E**) and case B left eye (**F**)

extensive disorganization of external retinal layers (Figs. 1, 2). Such items are also consistent with the electrophysiological testing of these cases. FF-ERG (Figs. 3, 4) showed both a diffuse affection of photoreceptors and bipolar cells, with a major impact on the cone system and an asymmetrical effect on scotopic responses, presenting with a reduced *a wave* altogether with a *b wave* in almost an electronegative configuration [6]. This lower *b* to *a* ratio could suggest a major effect on bipolar and Müller cells over photoreceptors that could be related to CSA/ERCC8 mutation. However, whether such a finding could be associated with retinal dysfunction, as some forms of congenital stationary night blindness, or with neurological affection, as some authors have recently claimed regarding optic neuromyelitis, is still to be fully elucidated [9, 10]. On the other hand, MF-ERG (Fig. 5) reported a wide disruption of signal that was only conserved, although diminished, in central areas of case A, which accordingly held better visual acuity than case B. In addition to these retinal findings, both retinal nerve fibre layer and ganglion cell layer were also decreased in the presented cases, therefore showing an existing neurological affection that is consistent with CS general understanding [1, 11].

In conclusion, our findings in these cases could be therefore considered of great importance since objectively detecting a wide electrophysiological retinal dysfunction in CS. Moreover, such affection seems to be much more severe according to functional tests than as per damaged retinal area by eye fundus appearance, even though ultra-wide-field autofluorescence in fact detects extensive and diffuse retinopathy. In addition, reported dysfunction of the cone system could explain macular atrophy and progressive vision loss beyond peripheral pigmentary retinopathy that could be, on the other hand, mainly linked to rod affection. Finally, the asymmetrical disruption of scotopic response with a lower *b* to *a* ratio could suggest a specific pathologic effect of CSA/ERCC8 mutation on neuronal and retinal cells; however, such findings need to be further confirmed in extensive future case series studies. As a whole, our presented case reports newly provide important results, both functional and anatomical, on retinal abnormalities of CS with the latest cutting-edge ophthalmic diagnostic techniques.

Compliance with Ethical Standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with a financial interest (such as honoraria; educational grants; participation in speaker's bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationship, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statement of the welfare of animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Patients and their next of kin have provided written informed consent for the submission of the case report to the journal.

References

1. Karikkineth AC, Scheibye-Knudsen M, Fivenson E, Croteau DL, Bohr VA (2017) Cockayne syndrome: clinical features, model systems and pathways. Ageing Res Rev 33:3–17
2. Laugel V, Dalloz C, Durand M, Sauvanaud F, Kristensen U, Vincent MC et al (2010) Mutation update for the CSB/ERCC6 and CSA/ERCC8 genes involved in cockayne syndrome. Hum Mutat 31(2):113–126
3. Wu Y, Zheng Y, Yan X, Huang Y, Jiang Y, Li H (2017) Ocular findings in a patient with cockayne syndrome with two mutations in the ERCC6 gene. Ophthalmic Genet 38(2):175–177
4. Laugel V (1993) Cockayne syndrome. In: Pagon RA, Adam MP, Ardinger HH (eds) Gene reviews. University of Washington, Seattle
5. Hood DC, Bach M, Brigell M, Keating D, Kondo M, Lyons JS et al (2012) ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). Doc Ophthalmol 124(1):1–13
6. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R et al (2015) ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol 130(1):1–12
7. Scaioli V, D'Arrigo S, Pantaleoni C (2004) Unusual neurophysiological features in Cockayne's syndrome: a report of two cases as a contribution to diagnosis and classification. Brain Dev 26(4):273–280
8. Trese MGJ, Nudleman ED, Besirli CG (2017) Peripheral retinal vasculopathy in cockayne syndrome. Retin Cases Brief Rep 11(3):232–235

9. Zeitz C, Robson AG, Audo I (2015) Congenital stationary night blindness: an analysis and update of genotype-phenotype correlations and pathogenic mechanisms. Prog Retin Eye Res 45:58–110
10. You Y, Zhu L, Zhang T, Shen T, Fontes A, Yiannikas C et al (2019) Evidence of Müller glial dysfunction in patients with aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder. Ophthalmology. https://doi.org/10.1016/j.ophtha.2019.01.016
11. Rapin I, Weidenheim K, Lindenbaum Y, Rosenbaum P, Merchant SN, Krishna S et al (2006) Cockayne syndrome in adults: review with clinical and pathologic study of a new case. J Child Neurol 21(11):991–1006