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Chromosomal aberrations in cerebral visual impairment

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ABSTRACT

Background: Cerebral visual impairment (CVI) is a disorder in projection and/or interpretation of the visual input in the brain and accounts for 27% of the visually impaired children.

Aim: A large cohort of patients with CVI was investigated in order to ascertain the relevance of chromosomal aberrations in the etiology of this disorder.

Methods: 607 patients with CVI and a visual acuity ≤0.3 were assessed for the presence of a chromosomal aberration retrospectively. The observed aberrations were classified for pathogenicity.

Results: A total of 98 chromosomal aberrations were found in 79 persons (13%) of the cohort.

In nine persons it was not possible to classify the clinical implication of the aberration, due to lack of detailed information. In 70 persons it was possible to classify the aberration for causality: in 41 patients the aberration was associated with CVI, in 16 it was unknown and in 13 the aberration was unlikely to be associated with CVI. For four aberrations, present in 26 patients, the association with CVI has been reported before: trisomy 21, 1p36 deletion syndrome, 17p13.3 deletion syndrome (Miller-Dieker syndrome) and 22q13.3 deletion syndrome (Phelan-McDermid syndrome). The chromosomal aberrations in another 15 patients were for the first time associated with CVI.

Conclusions: Chromosomal aberrations associated with CVI were found in 7% (41/607) of patients, of which 37% (15/41) have not been reported before in association with CVI. Therefore, in patients with CVI chromosomal investigations should be routinely performed to warrant a good clinical diagnosis and counseling.

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1. Introduction

Cerebral visual impairment (CVI) is one of the major causes of visual impairment in the developed world, as it accounts for 27% of low vision in childhood.[1,2] It includes all visual dysfunctions caused by damage to, or malfunctioning of, the retrochiasmatic pathways in the absence of damage to the anterior visual pathways or any major ocular disease.[3,4] CVI is diagnosed when no ocular abnormality can explain the impairment in vision. This impairment can consist of a reduced visual acuity, and/or visual field defects.[5] Furthermore, there can be an abnormal visual behavior, such as staring into light or delayed fixation. Deficits in higher perceptual functions, for example difficulties with recognition of objects and faces, or visio-spatial disorders can occur, and are sometimes the only features of CVI.[6–8] The prevalence of persons with CVI without a severe visual acuity loss or visual field defects is unknown.

An important cause of CVI is acquired damage to the brain, mainly the result of perinatal problems, such as cerebral hemorrhage or periventricular leucomalacia. Cerebral damage during the prenatal (e.g. congenital CMV infection), neonatal (e.g. hypoglycemia) and childhood (e.g. meningitis or head trauma) period are less frequent causes of CVI.[5] Furthermore, West syndrome and hydrocephalus can result in CVI.[9–11] So far, less attention has been paid to genetic causes of CVI, although several neurodegenerative causes have been described.[12]

CVI is often part of a more complex phenotype, consisting of intellectual disability, epilepsy and/or deafness.[4,13,14] Recently, the awareness is growing that CVI is common in intellectual disability and in a large cohort of 923 patients with intellectual disability visual impairment due to CVI was present in 5%.[15] In patients with intellectual disability a causative chromosomal aberration can be found in about 5–30%, depending on the resolution of the technique used and the cohort selected.[16–20] Since 1970 karyotype analysis has been used to detect chromosomal aberrations larger than 5 Mb, but since the introduction of array-based comparative genomic hybridization (array CGH) techniques around ten years ago, the resolution increased significantly allowing the detection of causative aberrations as small as 20 kb. Besides intellectual disability also other neurocognitive disorders, such as autism and schizophrenia, can be caused by chromosomal aberrations.[21] Moreover, recently, deletions of 5q15 including the *NR2F1*-gene were described to cause CVI.[22] This initiated our study to ascertain to what extend chromosomal aberrations can be the underlying cause of CVI. Here we provide an overview of the chromosomal aberrations found in the largest cohort of patients with CVI described so far.

2. Methods

All patients diagnosed with CVI were seen and tested in Bartiméus, an institute for diagnostics, rehabilitation and schooling of the visually impaired in the Netherlands. CVI was diagnosed by a pediatric ophthalmologist under the following criteria: no other ocular diagnosis which could explain the visual impairment or visual field defect, and/or typical features such as poor fixation or crowding, and/or CVI found at neuropsychological investigation. Neuropsychological investigation was, however, not possible in a majority of the individuals, because of their developmental age. The individuals with CVI included in this study underwent their first ophthalmological examinations between 1-1-1993 and 1-1-2013. Additional inclusion criteria were low vision, defined as a visual acuity of $\leq$0.3 or <9.8 cycles/cm at 55 cm or a visual field of 30° or below.[2] Under the age of three the visual acuity was measured by Teller Acuity Cards and defined as decreased, when the cycles/degree were below the standard deviation reported by Courage and Adams.[23] Visual acuity in young children or in individuals with a young developmental age was measured by preferential looking (Teller Acuity Cards, 55 cm), Cardiff cards (1 m), picture optotypes (mainly LH Symbols at 3 m), or number optotypes (6 m). The confrontational method with white Stycar balls, 5 cm in diameter, was used to estimate the visual field. Exclusion criterion was a second ocular diagnosis causing low vision, such as cataract, retinopathy of prematurity, congenital nystagmus, or primary (hereditary) optic atrophy. All medical correspondence of the patients with CVI was screened for chromosomal investigations. For all patients with a chromosomal aberration the available clinical data were screened for risk factors for CVI, which are perinatal problems, periventricular leucomalacia, stroke, West syndrome, hydrocephalus, hypoglycemia or a gestational age <37 weeks. In addition, the results of the most recent ophthalmologic examination were collected, including binocular visual acuity, visual fields, strabismus, nystagmus, refraction error and the appearance of the optic disc. All chromosomal aberrations were classified for pathogenicity for CVI according to an adapted workflow of Koolen et al. (Fig. 1).[19] The database of genomic variants (http://dgv.tcag.ca/dgv/app/home) was used to filter against common variants. When no cerebral damage or other risk factor was found to explain CVI it was assumed that the chromosomal aberration was possibly associated with CVI.

3. Results

Of the 607 individuals with CVI and a visual acuity of $\leq$0.3, 197 (32%) had undergone chromosomal investigations, either karyotype analysis ($n = 109$) or array CGH ($n = 75$). In 13 patients the method was not specified. In 79 patients (79/607, 13%) 98 aberrations were found (Supplementary Table 1). The phenotype of these patients is described in Supplementary Table 2. Three patients (patients 12, 41 and 45) have been reported previously.[24–26] For ten aberrations it was not possible to obtain the exact breakpoints of the aberration. In addition, the clinical interpretation proved to be difficult for four aberrations. First, a del(22)(p11.1) deletion, patient 1, this region contains no genes and was therefore not classified. Secondly, a small duplication dup(6)(p25.3p25.2) in patient 47, was of unknown inheritance. This gain contains partly the *GMDS*-gene, GDP-mannose 4,6-dehydratase. It is unknown whether