



Published in final edited form as:

Am J Med Genet A. 2006 July 15; 140(14): 1504–1510. doi:10.1002/ajmg.a.31288.

An Autosomal Recessive Form of Spastic Cerebral Palsy (CP) with Microcephaly and Mental Retardation

Anna Rajab^{1,2,*}, Seung-Yun Yoo^{4,5,*}, Aiman Abdulgalil³, Salem Kathiri², Riaz Ahmed², Ganeshwaran H. Mochida^{4,5,6}, Adria Bodell^{4,5}, A. James Barkovich⁷, and Christopher A. Walsh^{4,5,§}

¹Genetic Unit, DGHA, Ministry of Health, Sultanate of Oman

²Department of Pediatrics, Royal Hospital, Muscat, Sultanate of Oman

³Pediatric Unit, Rustaq Regional Hospital, Rustaq, Sultanate of Oman

⁴Department of Neurology and Howard Hughes Medical Institute, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02115, U.S.A.

⁵Division of Genetics, Children's Hospital Boston, Boston, MA 02115, U.S.A.

⁶Pediatric Neurology Unit, Department of Neurology, Massachusetts General Hospital, Boston, MA 02115, U.S.A.

⁷Department of Radiology, University of California San Francisco, San Francisco, CA 94143, U.S.A.

Abstract

Cerebral palsy (CP) is defined as any nonprogressive motor deficits resulting from cerebral abnormalities that occur in the prenatal or perinatal period. Symptoms become apparent during the first year of life. Genetic forms of CP account for about 2% in European populations but are thought to cause a substantial proportion in consanguineous families. We have identified a large consanguineous family from Oman with spastic diplegia, microcephaly, and mental retardation. Additional manifestations include hyperreflexia, clumsiness, unstable gait, drooling, and dysarthria. There was phenotypic variability among different individuals, but spastic diplegia, microcephaly, and mental retardation were three constant traits present in all affected individuals.

Keywords

spastic diplegia; microcephaly; mental retardation; autosomal recessive inheritance

Introduction

Cerebral palsy (CP) is a large group of disorders impairing control of movement due to a defect or lesion of the developing brain. Symptoms become apparent within the first few years of life and generally do not worsen over time [Hughes and Newton, 1992]. It is a common disorder of childhood, with an incidence of 1 in 250 to 1,000 births [Bunday and Alam, 1993; Pharoah et al., 1987]. Individuals with CP may have difficulty in fine motor skills, maintaining balance and walking, or have involuntary movements such as

§Correspondence to: Christopher A. Walsh, 77 Avenue Louis Pasteur, NRB Room 266, Boston, MA 02115, U.S.A.; e-mail: cwalsh@bidmc.harvard.edu.

*These authors contributed equally to this work.

uncontrollable writhing motions of the hands or drooling. Some patients may also have mental retardation and seizures, and some children with CP are born with an abnormally small head (microcephaly) [NINDS, 2005].

CP is divided into four main categories: spastic, athetoid, ataxic, and mixed forms, according to the type of movement disturbance [Hughes and Newton, 1992; NINDS, 2005]. Spastic CP accounts for approximately 70-80% of cases, and is subdivided into hemiplegic, diplegic, quadriplegic, and monoplegic types, depending on which limbs are affected. Spastic CP patients show increased deep tendon reflexes, hypertonia, and weakness. Scissors gait is common. The most severe form of spastic CP, spastic quadriplegia is frequently accompanied by dysarthria. Athetoid and ataxic CP comprise 10-20% and 5-10% of cases, respectively. The most common mixed forms are spasticity and athetoid movements, but other combinations are also possible [NINDS, 2005].

The cause of CP is often hard to determine but about 10-15% of cases appear to be due to intrapartum problems [Blair and Stanley, 1988]. The other major risk factors are prematurity, small size for gestational age, and multiple births [Stanley, 1994]. Inherited factors are thought to contribute to approximately 2% of cases in European populations [Hughes and Newton, 1992; Mitchell and Bunday, 1997]; however, with increased understanding of genetic patterns that cause neonatal brain disorders, it is clear that *de novo* mutations and recessive disorders can often simulate “nongenetic” conditions. A study of CP prevalence in Asian (almost exclusively from Northern Pakistan) and non-Asian populations in Yorkshire, United Kingdom has reported a two-fold increase in CP prevalence in the Asian population (6.42 cases per 1,000) compared to non-Asian population (3.18 cases per 1,000) [Sinha et al., 1997]. Since about 60 % of the Asian families in this study had a known history of consanguineous marriages, and since about a third of the affected children in these families had a first or second degree relative with the same type of CP, recessive genes may have caused the increased incidence. An independent study from Saudi Arabia reported a 2.5-fold increase in the occurrence of CP in consanguineous families [Al-Rajeh et al., 1991], also strongly suggesting that the recessive forms of CP exist.

A genetic form of spastic CP with microcephaly and mental retardation has previously been described in the literature [Adler, 1961; Bunday and Griffiths, 1977; Gustavson et al., 1989; Mitchell and Bunday, 1997]. All patients were born to healthy consanguineous parents and have affected sibling(s). Autosomal recessive inheritance was predicted in most cases; however, no causative gene has been identified.

Here we report on a detailed clinical description of a large consanguineous family from Oman showing spastic CP with microcephaly and mental retardation. Our analysis provides evidence that a heritable factor causes these symptoms in this family, and reiterates the importance of recessive genes as a cause of CP.

Patients and Methods

Clinical studies

We examined a large consanguineous family from the Sultanate of Oman. Ten relatives exhibited spastic diplegia, microcephaly, and mental retardation. Forty-four members of the family were examined independently by A.R. and G.H.M., and the imaging studies were reviewed independently by A.J.B. and C.A.W.

Results

The pedigree is shown in Fig. 1. The parents are of Omani origin. The extensive consanguinity and the involvement of children of both sexes strongly suggest autosomal recessive inheritance. All patients were born at term after a normal pregnancy. None had a history of asphyxia, hypoglycemia, or other perinatal complications. In general, patients were hypotonic as infants. They showed delayed psychomotor and speech development. The clinical findings are summarized in Tables I and II.

Example case histories

Here we describe three affected siblings (Patient 1, 2, and 3) in detail as representative cases followed by a summary of rest of the patients.

Patient 1—The proband is a 16-year-old young man who was born at full term after an uncomplicated pregnancy via a normal spontaneous vertex delivery. There were no perinatal complications. He is the sixth of eight siblings and has two similarly affected sisters and five healthy siblings (Fig. 1). The occipito-frontal circumference (OFC), length, and weight at birth were 33cm (9th centile), 47cm (13th centile) and 2.85kg (12th centile), respectively. He was hypotonic as an infant and showed a delay in acquiring developmental milestones. He crawled at age two and started to walk at age three. His speech was significantly delayed. There were no hospitalizations or major illnesses during childhood.

Examination at the age of 16 showed a teenager with mental retardation, severe microcephaly, and abnormal craniofacial features including low frontal and temporal hairlines and simple ears. His height was 140cm (-4.66SD), weight 27kg (-4.04SD), and OFC 45cm (-6.67SD). He showed drooling, dysarthria, and hand movements that were clumsy and dysmetric. He exhibited exaggerated deep tendon reflexes and increased tone in all four limbs; however, the lower limbs were more severely affected than the upper ones. He was unable to run fast and tended to fall with fast walking or turning. There were no joint contractures. Hearing, vision, and cardiac examinations were normal. Abdominal ultrasonographs and skeletal radiographs were normal. Results of laboratory tests, including hematological parameters, serum biochemical parameters, thyroid hormone, serum amino acids, urinary organic acids, and chromosomal analysis, were normal. Brain MRI showed no structural anomalies other than microcephaly.

Patient 2—Patient 2 is the younger sister of Patient 1 and was born at full term with OFC, length, and weight of 34cm (32nd centile), 48cm (33th centile), and 2.5kg (4th centile), respectively. She was hypotonic and showed continuous tremors on the right side of the body. Developmental milestones were delayed. At six months, she experienced a febrile seizure, after which she continued to experience afebrile generalized tonic-clonic seizures that were controlled with sodium valproate. She started to walk around the age of six with the help of physical therapy.

At the age of 15, she was a small teenager with craniofacial abnormalities similar to those of Patient 1. Her OFC, height, and weight were 48cm, (-3.25SD), 141cm (-3.08SD), and 40kg (-1.68SD), respectively. She had severe mental retardation. Her eye movements were slow, but vision was normal. There were no fundoscopic abnormalities. She also showed drooling and dysarthria. She had tremulous hand movements, more pronounced on the right side than on the left. Neurological examination showed bilateral pyramidal signs with increased deep tendon reflexes, brisker on the right side. Her gait was clumsy and unsteady. There was nonprogressive spasticity of the lower limbs. An EEG showed sharp discharges from the temporal regions bilaterally. Abdominal ultrasonographs and skeletal radiographs were normal. Results of laboratory tests, including hematological parameters, serum biochemical

parameters, thyroid hormone, serum amino acids, urinary organic acids, and chromosomal analysis, were normal.

Patient 3—This patient is the younger sister of Patient 1 and 2. She was born at full term by a normal spontaneous vertex delivery. There were no perinatal complications. Measurements at birth showed OFC of 33cm (13th centile), length of 49cm (43th centile), and weight of 2.5kg (7th centile). The mother noted the absence of head control at the age of five months. Examination at six months showed OFC of 37cm (-4.36SD), length of 65cm (36th centile), and weight of 6kg (8th centile).

At the age of 11, her craniofacial features were similar to those of Patient 1 and 2. Her OFC, height, and weight were 46cm (-4.3SD), 115cm (-4.29SD), and 15kg (-3.5SD), respectively. She has mental retardation, but her social development and bonding skills were satisfactory. She was dysarthric, and her speech was limited to single words indicating simple needs. There were exaggerated deep tendon reflexes and increased tone in all limbs. Abdominal ultrasonographs and skeletal radiographs were normal. Results of laboratory tests, including hematological parameters, serum biochemical parameters, thyroid hormone, serum amino acids, urinary organic acids, and chromosomal analysis, were normal. MRI was normal other than microcephaly (Fig. 2E), and EEG was unremarkable.

Other Patients—Other patients that are not described here were similar to Patient 1, 2, and 3 (Tables I and II). They were born at full term after uncomplicated pregnancies without perinatal complications. Symptoms became noticeable around six months of age. All were born with a normal head size, but OFC dropped below the 3rd centile during the first six months after birth. The affected individuals also had brachycephaly and low anterior and temporal hairlines (Fig. 2A-D). Brain MRI of Patient 5 showed microcephaly with no other structural abnormalities similar to Patient 3 (Fig. 2F). Mental retardation was apparent. Patients 4 and 10 had fallen from the roof of the house when they were seven and three years old, respectively. Patient 10 recovered from the injury, but Patient 4 became wheelchair-bound, lost vision in the left eye, and developed seizures. Three patients (Patients 2, 4, and 7) experienced prolonged febrile seizures during their early childhood and later developed epilepsy. All patients were shorter and lighter compared to unaffected siblings.

Discussion

The consanguineous family we described shows an apparent genetic form of spastic CP with microcephaly and mental retardation. The inheritance of this syndrome in this family fits well with an autosomal recessive trait: parents were consanguineous and normal, and children of both sexes were affected in each sibship. Symmetrical spastic diplegia with brisk tendon reflexes were unifying features but differed in severity and were asymmetric in one patient (Patient 2) (Table II). Symmetry of neurological signs is frequently observed in familial cases of spastic CP-like syndromes [Böök, 1953; Mitchell and Bunday, 1997; Yannet, 1949]. Most patients showed scissors gait due to spasticity in lower limbs, but it was not apparent in preschool children (Table II). Patients had well-integrated personalities in general. There were no difficulties in swallowing, no abnormalities of cranial nerves, and no evidence of neuropathy. There were no cerebellar signs such as nystagmus and broad-based gait, but the patients manifested clumsy and tremulous hand movements. In the upper limbs, brisk tendon reflexes were found in a majority of patients but no spasticity or contractures. Deterioration of walking and progressive contractures of lower limbs were seen in three adult patients (Patient 4, 8, and 10). It is not clear if contractures were part of the syndrome or resulted from long-standing spasticity of the limbs.

Several studies have previously described patients with similar symptoms as the family presented here [Adler, 1961; Bunday and Griffiths, 1977; Fisher and Russman, 1974; Gustavson et al., 1969; Gustavson et al., 1989; Mitchell and Bunday, 1997]. Some of these cases were sporadic [Fisher and Russman, 1974; Gustavson et al., 1969], but most of them exhibited clear autosomal recessive inheritance [Adler, 1961; Bunday and Griffiths, 1977; Gustavson et al., 1989; Mitchell and Bunday, 1997]. The clinical spectrum was quite diverse even within the same family; microcephaly, mental retardation, and epilepsy were variable features. Interestingly, although severity of disease varied among different individuals, microcephaly and mental retardation were invariably present in all of our patients.

McHale and colleagues have used homozygosity mapping to identify a genetic locus responsible for spastic CP in eight consanguineous families from Mirpur region of Pakistan [McHale et al., 1999]. The affected children in this study exhibited symmetrical, nonprogressive spasticity, and no adverse perinatal history or known alternative underlying diagnosis. Three families showed a linkage to 2q24-25 [McHale et al., 1999]. One of these families (Family 8) had symptoms similar to those of our patients but they were diagnosed as having early onset hereditary spastic paraplegia [Mitchell and Bunday, 1997]. In the other two families, microcephaly was a variable feature. One family that does not map to 2q24-25 (Family 6) shares the most symptoms to the family described here. Their symptoms were more severe in that all four limbs were spastic, but microcephaly and mental retardation were also present in both patients [McHale et al., 1999; Mitchell and Bunday, 1997].

We have performed a genomewide linkage screen of the family reported here and ruled out linkage to 2q24-25 (Yoo S.-Y. and Walsh, C.A.W., unpublished data). We found some evidence of linkage to a distinct locus other than 2q24-25; however, we found no site in the genome where all of the patients share haplotypes, making this linkage not yet definitive. One possible explanation would be that although all 10 patients are clinically indistinguishable, the symptoms in one or two patients might have different origin, or might not be genetic.

Although genetic forms of CP tends to be rare, our report, together with the previous findings, suggests that there may be a number of recessively inherited disorders that give a rise to spastic CP-like syndrome with nonprogressive spasticity, microcephaly, and mental retardation. Identification of gene(s) involved in these disorders will provide an unique opportunity to understand the underlying mechanisms of CP.

Acknowledgments

We thank the patients and their families for their participation in this study; Dr. Miguel Fiol for his kind assistance in performing neurologic examination in the patients; and Drs. Annapurna Poduri and Bernard S. Chang for critical reading of the manuscript. This work was supported by a National Alliance for Autism Research (NAAR) Postdoctoral Fellowship to S.-Y.Y. and NINDS grant 2R37NS35129 to C.A.W. C.A.W. is an Investigator with the Howard Hughes Medical Institute.

References

- Adler E. Familial cerebral palsy. *J Chronic Dis.* 1961; 13:207–214. [PubMed: 13681498]
- Al-Rajeh S, Bademosi O, Awada A, Ismail H, Al-Shammasi S, Dawodu A. Cerebral palsy in Saudi Arabia: a case-control study of risk factors. *Dev Med Child Neurol.* 1991; 33:1048–1052. [PubMed: 1778341]
- Blair E, Stanley Fj. Intrapartum asphyxia: a rare cause of cerebral palsy. *J Pediatr.* 1988; 112:515–519. [PubMed: 3351675]

- Böök, Ja. A genetic and neuropsychiatric investigation of a North-Swedish population with special regard to schizophrenia and mental deficiency. II. Mental deficiency and convulsive disorders. *Acta Genet Stat Med.* 1953; 4:345–414. [PubMed: 13137900]
- Bundey S, Alam H. A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding. *Eur J Hum Genet.* 1993; 1:206–219. [PubMed: 8044647]
- Bundey S, Griffiths Mi. Recurrence risks in families of children with symmetrical spasticity. *Dev Med Child Neurol.* 1977; 19:179–191. [PubMed: 870357]
- Fisher, RI; Russman, Bs. Genetic syndromes associated with cerebral palsy. *Clin Orthop Relat Res.* 1974; 99:2–11. [PubMed: 4825718]
- Gustavson, Kh; Hagberg, B.; Sanner, G. Identical syndromes of cerebral palsy in the same family. *Acta Paediatr Scand.* 1969; 58:330–340. [PubMed: 5824822]
- Gustavson, Kh; Modrzewska, K.; Erikson, A. Hereditary spastic diplegia with mental retardation in two young siblings. *Clin Genet.* 1989; 36:439–441. [PubMed: 2591069]
- Hughes I, Newton R. Genetic aspects of cerebral palsy. *Dev Med Child Neurol.* 1992; 34:80–86. [PubMed: 1544520]
- Mchale, Dp; Mitchell, S.; Bundey, S.; Moynihan, L.; Campbell, Da; Woods, Cg; Lench, Nj; Mueller, Rf; Markham, Af. A gene for autosomal recessive symmetrical spastic cerebral palsy maps to chromosome 2q24-25. *Am J Hum Genet.* 1999; 64:526–532. [PubMed: 9973289]
- Mitchell S, Bundey S. Symmetry of neurological signs in Pakistani patients with probable inherited spastic cerebral palsy. *Clin Genet.* 1997; 51:7–14. [PubMed: 9084927]
- Ninds. *Cerebral Palsy: Hope Through Research.* NINDS. 2005
- Pharoah, Po; Cooke, T.; Rosenbloom, I.; Cooke, Rw. Trends in birth prevalence of cerebral palsy. *Arch Dis Child.* 1987; 62:379–384. [PubMed: 3592729]
- Sinha G, Corry P, Subesinghe D, Wild J, Levene Mi. Prevalence and type of cerebral palsy in a British ethnic community: the role of consanguinity. *Dev Med Child Neurol.* 1997; 39:259–262. [PubMed: 9183266]
- Stanley, Fj. The aetiology of cerebral palsy. *Early Hum Dev.* 1994; 36:81–88. [PubMed: 8200323]
- Yannet H. Infantile cerebral palsy cases with severe mental deficiency. *Pediatrics.* 1949; 3:820–823. [PubMed: 18131833]

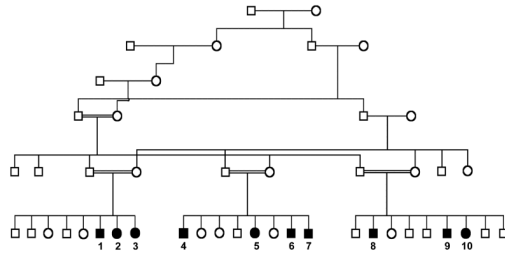


Figure 1.

Pedigree structure of the family. There is a high frequency of consanguineous marriage in this family. Patients described in this study are numbered. Squares and circles indicate males and females, respectively. Affected individuals are shown as filled symbols. The parents of patients are not listed on the order of birth for the sake of viewing.

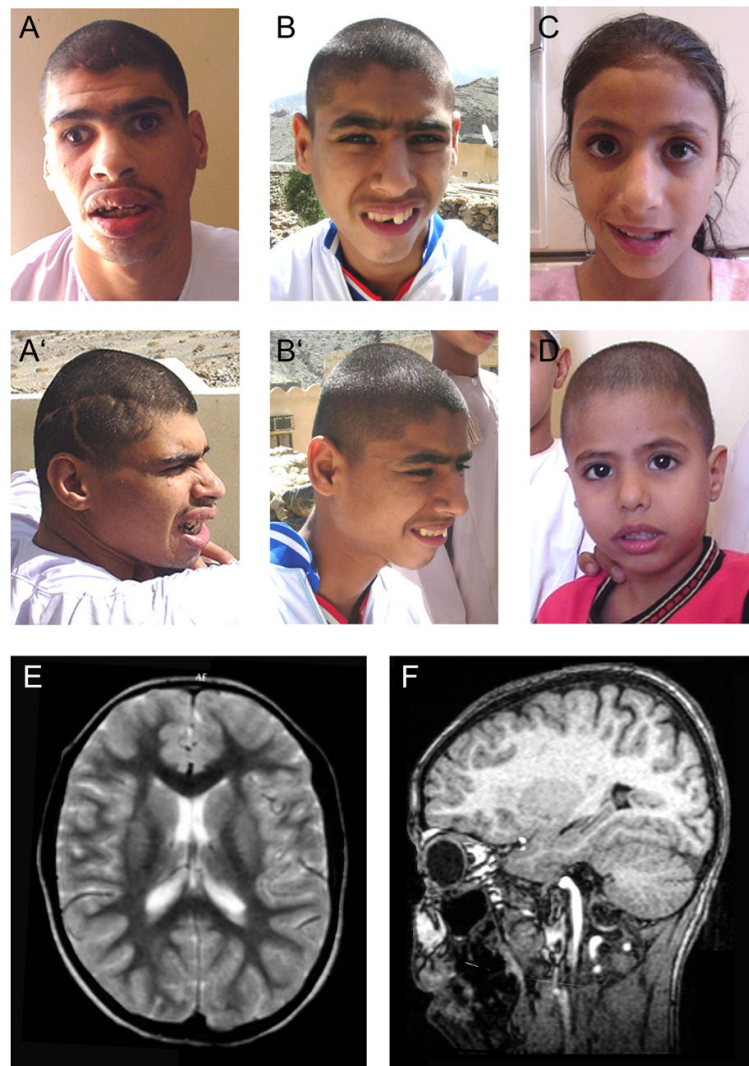


Figure 2. Craniofacial morphologies and MRI of the patients with spastic CP. Craniofacial morphologies of Patient 4 (A and A'), 9 (B and B'), 5 (C), and 6 (D) showing microcephaly, brachycephaly, and low anterior and temporal hairlines. (E) Brain MRI of Patient 3. Conventional spin-echo MR imaging of the brain was performed in multiple planes. This T2-weighted axial image demonstrates the presence of a normal gyral pattern, normal white matter signal, normal basal ganglia, and normal ventricular morphology and size. (F) Brain MRI of Patient 5. Conventional spin-echo MR imaging of the brain was performed in multiple planes. This T1-weighted parasagittal image demonstrates a craniofacial disproportion suggestive of microcephaly. No other abnormalities of brain anatomy are seen.

Table I
Common craniofacial and neurological manifestations

Common Craniofacial Findings	Common Neurological Traits
Postnatal microcephaly	Nonprogressive spasticity in lower limbs
Brachycephaly	Clumsiness
Low anterior and temporal hairlines	Tremulous hand movements
Mild sloping of forehead	Unsteady gait
Simple ears	Delayed developmental milestones
	Dysarthria

All 10 patients exhibited these symptoms. Severity of each symptom varied among different individuals.

Table II

Variable Neurological Manifestations

Patient number	Current age	Brisk deep tendon reflexes		Increased tone		Ankle clonus	Extensor plantar response	Joint contractures in lower limbs	Seizures	Scissors gait	Additional Features
		Upper limbs	Lower limbs	Upper limbs	Lower limbs						
1	16	Y	Y	Y	Y	N	N	N	N	Y	
2	15	N	Y	N	Y	N	Y	N	Y ¹	Y	The right side showed more severe spasticity than the left
3	11	Y	Y	Y ²	Y	N	N	N	N	Y	No drooling
4	21	Y ³	Y ³	Y	Y	Y	Y	Y	Y ¹	N/A	Fell from the roof of the house at the age of seven, became a wheelchair-bound, and lost vision on the left eye
5	12	Y	Y	Y	Y	Y	N	N	N	Y	
6	7	Y	Y	Y	Y	N	N	N	N	N	Kyphoscoliosis
7	4	Y	Y	N	Y	Y	N	N	Y ¹	N	Mild intention tremor
8	28	Y	Y	N	Y	Y	Y	Y	N	Y	Mild intention tremor
9	17	N	Y	N	Y	Y	N	N	Y	Y	Experienced febrile seizures at the age of two for nine days but no seizures afterwards
10	16	Y	Y	Y ⁴	Y ⁴	Y	Y	Y	N	Y	Fell from the roof of the house at the age of three, no bladder or bowel control

¹ Seizures started as febrile seizures and developed into generalized tonic-clonic seizures

² Mild

³ Right side is more affected than the left

⁴ Left side is more affected than the right

Y=Yes and N=No

N/A=not applicable