Patterns of inheritance in familial ALS

Abstract—We investigated 185 families with ALS for evidence of anticipation and mitochondrial inheritance. Although initial analysis demonstrated significant anticipation of age at death between generations in patients with familial ALS, further analysis demonstrated features of regression to the mean, suggesting that the perceived differences are the result of bias. In addition, there was no evidence of an effect of preferential maternal inheritance, which would have supported transmission of mitochondrial DNA mutations.

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Marcus Bradley, MRCP; Lloyd Bradley, MRCP; Jackie de Belleroche, PhD, FRCPath; and Richard W. Orrell, MD, FRCP

Anticipation is the tendency for a disease to demonstrate an earlier age at onset or increasing severity of symptoms in successive generations.[1,2] Apparent anticipation has been reported in five Japanese[3,4] and three Italian[5] families with ALS and copper/zinc superoxide dismutase (SOD1) mutations. An excess number of male-transmitting grandparents and great-grandparents, suggesting selection against a large expansion in the female gamete, has been reported.[6] We found no significant change using a similar analysis.[7] Bulbospinal muscular atrophy is a related motor neuron disease, with a trinucleotide repeat expansion in the androgen receptor gene, although anticipation is relatively rare.[8]

Mitochondrial abnormalities have been demonstrated in different tissues of patients with ALS.[9] Mitochondrial DNA disorders are usually maternally inherited and a maternal effect on inheritance would be expected, if mutations of mitochondrial DNA are causative.

Using a database of families with ALS,[10] we investigated patterns of inheritance for evidence of anticipation and preferential maternal inheritance.

Methods. We studied 185 families, with at least two individuals having typical features of ALS.[10] Individual transmissions between generations were identified. Intergenerational values were compared between generation 1 (G1) and generation 2 (G2) for each individual transmission. G1 comprised fathers, mothers, uncles, and aunts. G2 comprised sons, daughters, nephews, and nieces. The differences in age at onset, duration of disease, and age at death between G1 and G2 were calculated. For first-degree transmissions, the number of cases with maternal inheritance was compared with paternal inheritance.

Statistical analysis was performed with SPSS (version 9.0) for Windows (SPSS Inc.). Direct transmissions were those between first-degree relatives (mother/father and son/daughter), and indirect transmissions were those between second-degree relatives (uncle/aunt and nephew/niece). Analyses were also performed on those members of G1 below and above the median (i.e., the lower and upper 50% of G1) to identify the statistical phenomenon of regression to the mean, where anticipation may be demonstrated in the offspring of older parents.[1,2]

Results. A total of 160 first-degree intergenerational transmissions were identified. Mean age at death was 55.2 years (95% CI: 54.0 to 56.4 years; n = 503) and mean disease duration was 3.5 years (CI: 2.9 to 4.1; n = 227). There was no difference ($p > 0.05$) in age at death between patients with SOD1 mutations (53.9 years; CI: 51.4 to 56.4; n = 114) and those with none (55.6 years; CI: 54.3 to 56.9; n = 389) or duration of disease between patients with SOD1 mutations (4.9 years; CI: 3.4 to 4.6; n = 34) and those with none (3.3 years; CI: 2.7 to 3.9, n = 193).

Median age at death was compared between the two generations (table 1). For all transmissions, the Wilcoxon rank sum test demonstrated higher median age at death in G1 (55 years) than G2 (48 years) ($p < 0.001$). The significance was present when studying the upper ($p < 0.001$) and middle ($p < 0.001$) 50% (i.e., 25th to 75th centile) of the G1 range. When the lower 50% of G1 was studied, there was no significant difference ($p > 0.05$).

Comparing difference in age at death between first-degree G1 and G2 pairs for the whole sample, the 95% CI did not contain zero, indicating that age at death in G1 was significantly greater than G2 (figure). A greater deviation from zero occurred when including only the older 50% of G1, and a negative deviation with the younger 50% members of G1.

Frequency of positive (anticipation) and negative intergenerational differences was compared using χ^2 test (table 2). This demonstrated the phenomenon of regression to the mean, i.e., the older the members of G1, the more significant the tendency toward anticipation. Studying all samples, χ^2 test was positive for anticipation in all groups, with the exception of first-degree intergenerational transfer in families with SOD1 mutations. When studying the younger 50% of G1, there was no anticipation.

Comparing the frequency of maternal and paternal inheritance, in SOD1-positive and -negative families, χ^2 test demonstrated no difference in frequency of maternal and paternal transmissions, for both SOD1-positive and -negative families ($p > 0.1$). This indicates that parental sex has no effect on inheritance.

From the Department of Clinical Neurosciences (Drs. M. Bradley, L. Bradley, and Orrell), Royal Free and University College Medical School, University College London, London, England; and Department of Neuromuscular Diseases (Dr. de Belleroche), Imperial College School of Medicine, London, England.

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Address correspondence and reprint requests to Dr. Richard W. Orrell, Department of Clinical Neurosciences, Royal Free and University College Medical School, University College London, Rowland Hill Street, London NW3 2QG, England; r.orrell@rfc.ucl.ac.uk

Table 1 *Median values of age at death for G1 and G2 in families with ALS*

		All samples		Upper 50% of G1		Middle 50% of G1		Lower 50% of G1	
	n	G1	G2	G1	G2	G1	G2	G1	G2
All families	291	55	48	63	54	55	48	45	45
M/F/A/U		$p < 0.001$*		$p < 0.001$*		$p < 0.001$*		$p > 0.05$†	
All families	160	57	53	64	55	57	53	49	48
M/F		$p < 0.001$*		$p < 0.001$*		$p < 0.005$*		$p > 0.05$†	
All families	131	53	46	62	48	53	46	42	43
A/U		$p < 0.005$*		$p < 0.001$*		$p < 0.001$*		$p < 0.05$†	
All families	90	55	49	61	53	55	52	48	43
M		$p < 0.005$*		$p < 0.001$*		$p < 0.05$*		$p > 0.05$	
All families	70	58	56	66	58	58	56	50	53
F		$p < 0.05$*		$p < 0.001$*		$p < 0.05$*		$p > 0.05$†	
Non-SOD1	184	55	48	63	58	55	49	43	47
M/F/A/U		$p < 0.01$*		$p < 0.001$*		$p < 0.05$*		$p < 0.005$†	
Non-SOD1	110	57	52	63	53	56	52	50	50
M/F		$p < 0.05$*		$p < 0.001$*		$p < 0.01$*		$p > 0.05$†	
SOD1	107	56	48	67	55	56	48	48	45
M/F/A/U		$p < 0.001$*		$p < 0.001$*		$p < 0.001$*		$p > 0.05$	
SOD1	50	57	54	66	60	56	54	48	45
M/F		$p < 0.05$*		$p < 0.05$*		$p > 0.05$		$p > 0.05$	

* p Wilcoxon rank sum test, where G1 was greater than G2 ($p < 0.05$).
† G2 > G1.

G1 = generation 1; G2 = generation 2; M = mother; F = father; U = uncle; A = aunt; SOD1 = copper/zinc superoxide dismutase.

Discussion. The mean age at death and disease duration were similar to those in previous studies of ALS. Median age at death was lower in the second generation ($p < 0.001$) (see table). Mean difference in age at death between the two generations was positive (younger death in the second generation) (see figure) and the number of occasions that positive anticipation occurred was significant ($p < 0.001$) (see table 2). Significant differences were observed in median age, mean difference in age, and frequency of earlier age at death between the generations. This supports the concept of anticipation in patients with ALS.

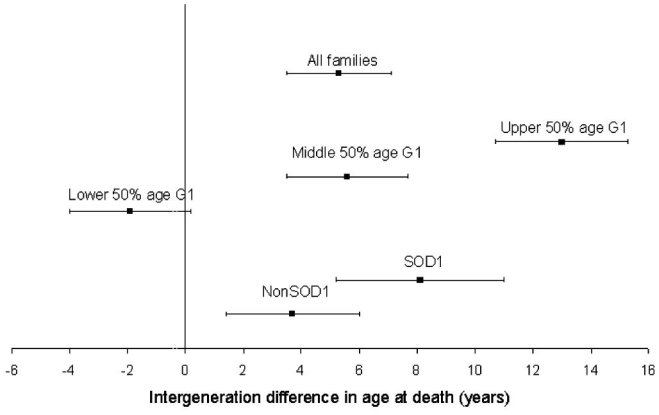

Figure. Intergeneration difference in age at death between generation 1 (G1) and generation 2 (G2), mean with 95% CI, for the upper, middle, and lower 50% of age of G1, and for copper/zinc superoxide dismutase (SOD1) and non-SOD1 families.

Ascertainment bias is recognized in studies of anticipation.[1,2] There is often incomplete information for age at onset because it may be difficult to precisely define the first feature of disease. Improvements in diagnostic capability and the increased family awareness once a parent is diagnosed, lead to offspring being diagnosed earlier than the parent. These forms of bias are avoided by using age at death.

Patients with a genetic disease may not wish or may be unable to have children, leading to bias due to reproductive fitness. An individual with early-onset disease may be less likely to have children. In a genetic line ending with early-onset patients, this will bias toward anticipation. Other studies used second-degree relatives to minimize this bias. Our analysis of second-degree relatives supported the presence of anticipation.

Ascertainment bias may occur if individuals are not interviewed at the same age. Simultaneous onset in both generations attracts the attention of family members and their physicians. G2 would have an earlier onset than G1, favoring anticipation. This is compounded because any siblings of G2 who eventually develop the disease, negating the effect of per-

Table 2 *Number of occasions when the difference between G1 and G2 is positive (anticipation) and negative*

		All samples		Top 50% of G1		Middle 50% of G1		Bottom 50% of G1	
	n	+	−	+	−	+	−	+	−
All families	291	182	109	118	23	100	49	65	87
M/F/A/U		18.29		∞		17.56		3.21	
		$p < 0.001$*		$p < 0.001$*		$p < 0.001$*		$p > 0.05$	
All families	160	101	59	67	14	53	32	35	46
M/F		11.02		∞		5.25		1.51	
		$p < 0.001$*		$p < 0.001$*		$p < 0.05$*		$p > 0.05$	
All families	131	81	50	56	10	41	23	26	41
A/U		7.34		16.27		5.1		3.41	
		$p < 0.01$*		$p < 0.001$*		$p < 0.05$*		$p > 0.05$	
All families	90	56	34	34	9	29	16	20	23
M		5.38		14.53		3.8		0.19	
		$p < 0.05$*		$p < 0.001$*		$p > .05$		$p > 0.05$†	
All families	70	45	25	31	4	21	14	15	22
F		5.71		21.36		1.4		1.36	
		$p < 0.05$*		$p < 0.001$*		$p > .05$		$p > 0.05$†	
Non-SOD1	184	108	77	70	12	58	35	38	65
M/F/A/U		5.22		∞		5.75		7.15	
		$p < 0.05$*		$p < 0.001$*		$p < 0.05$*		$p < 0.01$†	
Non-SOD1	110	70	41	49	6	38	21	21	35
M/F		7.65		∞		4.92		3.56	
		$p < 0.01$*		$p < 0.001$*		$p < 0.05$*		$p > 0.05$†	
SOD1	107	75	33	46	9	46	19	29	25
M/F/A/U		16.48		∞		11.39		0.296	
		$p < 0.001$*		$p < 0.001$*		$p < 0.001$*		$p > 0.05$	
SOD1	50	32	19	18	9	22	11	14	11
M/F		3.38		4.00		3.78		0.36	
		$p > 0.05$		$p < 0.05$*		$p > 0.05$		$p > 0.05$	

Chi-square and p values are given, for the null hypothesis that G1 = G2.

* Significant if $p < 0.05$.
† G2 > G1.

G1 = generation 1; G2 = generation 2; M = mother; F = father; U = uncle; A = aunt; SOD1 = copper/zinc superoxide dismutase.

ceived anticipation, would not be detected at the time of data collection.

Familial transmissions with SOD1 mutations would not be expected to demonstrate anticipation because the mode of inheritance is distinct from unstable trinucleotide repeat disorders. This suggests that apparent anticipation reported in SOD1 families[3–5] may represent regression to the mean rather than anticipation per se.

With no anticipation, the median value of G1 minus G2 will be close to zero, with CIs including zero. Regression to the mean is a phenomenon whereby higher values of G1 artificially increase the degree of perceived anticipation and vice versa for lower values of G1. This causes the value to be positive when selecting the oldest 50% of G1 and negative when selecting the youngest 50% of G1. The phenomenon was observed when we used this method to analyze the data (see figure). This suggests that the initial perception of anticipation is probably a result of regression to the mean. The possibility of anticipation in a small subgroup of families with ALS cannot be completely excluded.

We did not demonstrate increased maternal inheritance in familial ALS. The lack of sex effect on inheritance occurs in SOD1-positive and -negative families and does not support a major contribution of transmission of mitochondrial DNA mutations to inheritance.

In conclusion, there is an initial appearance of significant anticipation in age at death between generations in familial ALS. The absence of anticipation in the offspring of the younger half of the patient population studied raises the possibility of bias,

which is recognized in all anticipation studies. The recognition of apparent, but not true, anticipation, may be important in counseling families and affected individuals with ALS.

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Neuro*Images*

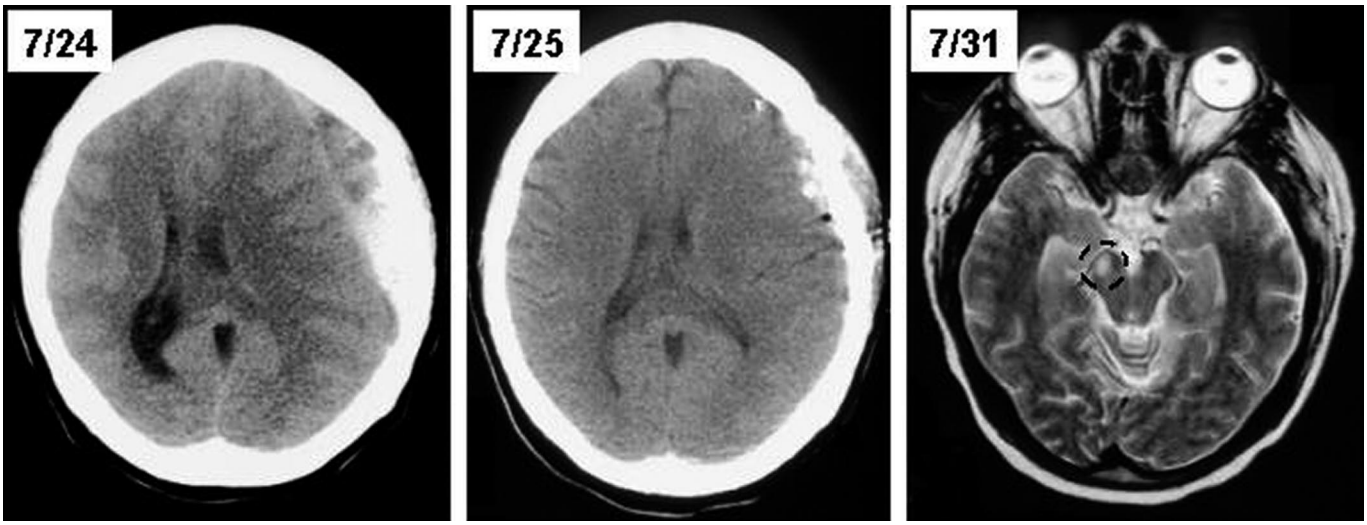

Figure. CT brain scan showed a left subdural hematoma with 1.5 cm midline shift (panel 7/24). After emergency platelet transfusion, the subdural hematoma was evacuated. Brain CT the next day showed resolution of the shift (panel 7/25). Brain MRI a week later showed a cerebral peduncle lesion in the T2-weighted sequence (panel 7/31). There was no history of head trauma.

Kernohan notch lesion after spinal tap

Harry Openshaw, MD, Duarte, CA

A 32-year-old woman with acute lymphocytic leukemia had abrupt onset of headache, decreased sensorium, and dilated left pupil. Lumbar punctures with intrathecal methotrexate had been done 4 and 7 days before her collapse. When she awakened from emergency evacuation of a subdural hematoma, there was ipsilateral hemiplegia and MRI showed a cerebral peduncle lesion (figure). Now, 32 months later, hemiparesis persists.

Subdural hematomas are rare complications of lumbar puncture, even in patients receiving intrathecal chemotherapy for leukemia.[1] The probable mechanism involves intracranial hypotension, subdural hygroma formation, stretching of the bridging veins, and bleeding in the context of thrombocytopenia. Kernohan notch hemiplegia may occur during transtentorial herniation. The lesion has been well explained anatomically,[2,3] but MRI demonstration and long-term patient survival are unusual.[4]

Address correspondence and reprint requests to Dr. Harry Openshaw, Department of Neurology, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010-3000; e-mail: hopenshaw@coh.org

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