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SHORT COMMUNICATION

Recurrent and fatal akinetic crisis in genetic-mitochondrial parkinsonisms

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Background and purpose: Akinetic crisis (AC) is the most severe and possibly lethal complication of parkinsonism. It occurs with an incidence of 3‰ Parkinson’s dis- ease patients per year, but it is not known whether genetically determined parkin- sonism is more or less susceptible to this complication.

Methods: In a cohort of 756 parkinsonian patients the incidence and outcome of AC was prospectively assessed. A total of 142 of the parkinsonian patients were tested for genetic mutations because of familial parkinsonism, and 20 patients resulted positive: in four the mutation deﬁnitely involved mitochondrial functions (POLG1, PINK1), two presented with LRRK2 mutation, nine presented with GBA mutation and ﬁve presented with Park 4 diﬀerent mutations.

Results: Akinetic crisis occurred in 30 patients for an incidence of 2.8‰ persons/ year and was lethal in seven (23%), not dissimilarly from known incidences of this complication. Yet six of 30 patients were carriers of genetic mutations, one GBA, one LRRK2, one POLG1 and three PINK1. In POLG1 and PINK1 carriers, the syndrome was recurrent and was fatal in three. Incidence of AC was 3.0‰ in famil- iar parkinsonism, 21.2‰ in genetic parkinsonisms.

Conclusions: Our preliminary ﬁndings suggest that the incidence of AC is remark- ably increased in carriers of these genetic mutations.

# Introduction

Akinetic crisis (AC), also termed malignant syndrome or Parkinson hyperpirexia syndrome, neuroleptic-like malignant syndrome or acute akinesia, is a complica- tion that appears in parkinsonism because of treat- ment manipulations or withdrawal, infectious diseases, trauma or gastrointestinal tract diseases [1]. AC is the most severe complication of PD occurring with an annual incidence of three cases per 1000 parkinsonian patients, and consists of acute motor symptom wors- ening characterized by an akinetic state with dyspha- gia, hyperthermia, increment of serum CPK and myoglobin, dysautonomia and transient unresponsive- ness to current antiparkinsonian treatment or to an increment of dopaminergic drug doses [1]. Its symp- toms are identical to symptoms of neuroleptic malig-

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nant syndrome [2,3], and it was hypothesized that both represent idiosyncratic severe complications induced by heterogeneous causes [4].

Cohort or multicenter studies highlighted the rele- vance of this complication of parkinsonism [1,5]. An operating deﬁnition of AC was also provided in order to facilitate diagnosis in patients already followed for their PD: ‘… sudden worsening of Uniﬁed Parkinson’s Dis- ease Rating Scale (UPDRS) motor score by 20 or more points, accompanied by three or more days of unrespon- siveness to the same drug regimen that adequately cor- rected symptoms before the appearance of akinesia or of unresponsiveness to rescue drugs’ (i.e. injectable apo- morphine, amantadine, levodopa esters) [1].

Yet in the last two decades several genetic muta- tions were identiﬁed in patients aﬀected by clinical PD, leading to a redeﬁnition of PD as a syndrome [6], including diﬀerent etiologies and some common clini- cal features.

No evidence was presented, however, on diﬀerences of AC prevalence in genetic rather than in ‘idiopathic’

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parkinsonisms, yet such information might be of rele- vance for an understanding of the mechanism of AC.

The occurrence of AC in six patients aﬀected by genetic parkinsonism due to mutations possibly or deﬁnitely involving mitochondrial function are described.

# Methods

The study is the prolongation of a previous study describing the incidence of AC in a cohort of 756 PD patients admitting only patients who were putatively diagnosed as aﬀected by PD according to UK Brain Bank criteria [7] (with the exception of the patient aﬀected by POLG1 mutation), who were regularly fol- lowed in our clinic, who were responsive to L-Dopa

[8] and who received evaluation assessments every 4– 5 months [including treatment titration, Hoehn and Yahr (H/Y) staging, UDPRS total score, Mini-Mental State Examination].

The present study is an incidental prospective cohort study, where incidence of AC and of genetic mutations were eventually matched.

The study was approved by our local ethical com- mittee (Comitato di Etica delle Province di Chieti- Pescara).

In order to reduce attrition due to drop-outs only patients who could be followed for at last 10 years were considered for the study (during the 2005–2013 time period 620 patients were occasionally addressed to our clinic but were not followed regularly). During follow-up 255 of the 756 patients died, and 86 patients were lost after the 10th year. Patient-year (PY) inci- dence calculations are added in the present study.

Of the 756 cohort patients, 142 presented with familial parkinsonism (76 with a ﬁrst degree relative involved); genetic testing was performed in all the 142 familial parkinsonisms and in two juvenile patients with no known familial transmission (yet both were tested negative).

Genetic testing was targeted according to the possi- ble mode of inheritance, age at onset and clinical pre- sentation of patients, on the following possible gene mutations: Park 8 (LRRK2) [exons 29, 31, 35, 41 (G2019S and I2020T) and 48]; GBA (p.L444P [c.1448 T>C], p.N370S [c.1926 A>G], E326K [c.1093 G>A]); Park 4 (SNCA [p.A53T], SNCB [p.L444P]). Pathoge-

netic mutations were identiﬁed in 20 patients from 19 families, including POLG1 (c.1288A > T transversion, c.2752T > C transition), mutation (*n* = 1), SNCA duplication (*n* = 2), SNCA triplication (*n* = 3); PINK1 p.G409V heterozygous mutations (*n* = 3); LRRK2 p.G2019S mutation (*n* = 2); GBA p.L483P, p.N409S and p.E365K heterozygous mutations (respectively

*n* = 3, *n* = 4 and *n* = 2). Genetic diagnosis was obtained 5 ± 2 years after admission to the AC cohort using standardized protocols [9–14]. The patient with POLG1 mutation is included in the study, despite the ambiguity of classiﬁcation, because of the potential signiﬁcance for the present report. He had been described in a previous paper [9] and had been followed for 10 years for progressive external ophthalmoplegia and ragged red ﬁber myopathy [9]. L-Dopa responsive parkinsonism appeared 15 years before death; the genetic diagnosis was provided 5 years before death due to AC.

*Post hoc* analysis evaluated whether phenotypic variables, UPDRS at admission, H/Y stage at admis- sion, treatments or presence of genetic mutations inﬂuenced the occurrence of AC, and whether the same variables inﬂuenced the outcome of AC, i.e. fatality or recovery.

AC occurrence

As reported in the previous study, only AC duration (in days) could predict the outcome (the longer the duration of AC, the higher the probability of fatal outcome). Other variables such as UPDRS scores, comorbidities at admission and during AC, progres- sion of disease, disease stage were equally distributed in patients with and without AC (Table 1). Disease duration was also similar, probably because of the method used to reduce attrition biases.

Table 2 shows that AC was observed in 30 of 756 cohort patients after a mean of 14.3 ± 2.7 years of follow-up (for a total of 10 828 PYs; overall incidence 2.8 9 1000 PYs). Of the 30 AC cases, 24 occurred amongst the 614 patients with non-familial PD (2.7 9 1000 PYs) and six in the 142 patients with familial PD (3.0 9 1000 PYs). The latter six cases were all diagnosed amongst the 20 patients with a genetic mutation (21.2 9 1000 PYs): four were carri- ers of genetic mutations involving the mitochondrial functions (one POLG1, three PINK1), one had LRRK2 mutation and one was a carrier of GBA mutation. The incidence of AC in non-genetically determined PD was 24 out of 736 patients (2.3 9 1000 PYs).

Fatalities due to AC occurred in seven of the 30 patients (23%); in three of the seven patients no genetic inheritance was in evidence; four of the seven were aﬀected by POLG1, PINK1 (two patients) and LRRK2 mutations.

One patient aﬀected by POLG1 mutation had three previous episodes of AC before the fatal last one; all the patients aﬀected by PINK1 had two or three epi- sodes of AC; two died in the last crisis.

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Table 1 Demographic and clinical data in PD patients with and without AC

H/Y Mean ± SD MMSE, mean ± SD Comorbidities

Cohort

Sample

*n*

Age, years mean ± SD

Disease duration\*

Admission

Last assessment

UPDRS,

mean ± SD

Admission

Last assessment

Cardiovascular no. of patients (%)

Metabolic no. of patients (%)

Autoimmune no. of patients (%)

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|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No AC | 726 | 67.6 ± 8.2 | 14.4 ± 2.9 | 1.5 ± 0.6 | 2.9 ± 0.7 | 11.0 ± 5.3 | 28.8 ± 1.5 | 25.6 ± 2.8 | 211 (29%) | 40 (5.5%) | 23 (3.1%) |
| AC |  |  |  |  |  |  |  |  |  |  |  |
| Non-familial PD | 24 | 66.8 ± 6.3 | 9.6 ± 3.1 | 1.3 ± 0.5 | 2.9 ± 0.6 | 10.8 ± 4.8 | 29.1 ± 0.8 | 27.7 ± 1.8 | 9 (37.5%) | 2(8.3%) | 1 (4.1%) |
| Genetic PD | 6 | 66.2 ± 7.5 | 10.1 ± 2.1 | 1.3 ± 0.4 | 2.8 ± 0.5 | 10.7 ± 4.1 | 29.2 ± 0.8 | 27.6 ± 2.3 | 2 (33.3%) | 0 | 0 |

AC, akinetic crisis; H/Y, Hoehn and Yahr stage; UPDRS, Uniﬁed Parkinson’s Disease Rating Scale part III; MMSE, Mini-Mental State Examination. Cardiovascular: hypertension, heart disease, venous disease, arteriopathy. Autoimmune: thyroiditis, rheumatoid arthritis. Metabolic: diabetes, dyslipidemia, blood urea nitrogen >20 mg/dl. H/Y and UPDRS are rated during optimized treat- ment according to need. When not diﬀerently stated, results refer to baseline condition.

\*For AC patients, disease duration is considered before AC.

Table 2 Incidence of akinetic crisis (AC) in the study population

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sample  Cohort *n* | | Age,  mean ± SD, years | Total follow-up, years mean ± SD | AC  *n* | Disease duration before AC, years mean ± SD | AC incidence (91000 PY)  IR (95% CI) | Recurrent AC no. of patients  (no. of recurrences) | Point increment UPDRS  Mean ± SD | Outcome |
| Overall sample of PD subjects with  ≥10 years of follow-up | 756 | 67.4 ± 6.3 | 14.3 ± 2.7 | 30 | 9.7 ± 3.4 | 2.8 (1.9–4.0) | 4 | 28.6 ± 14.3 | 7 fatal |
| Type of PD |  |  |  |  |  |  |  |  |  |
| Non-familial PD | 614 | 68.0 ± 7.2 | 14.4 ± 2.8 | 24 | 9.6 ± 3.1 | 2.7 (1.7–4.1) | 0 | 27.2 ± 15.3 | 3 fatal |
| Familial PD | 142 | 65.3 ± 3.5 | 14.2 ± 2.7 | 6 | 10.1 ± 2.1 | 3.0 (1.1–6.4) | 4 | 34.6 ± 8.9 | 4 fatal |
| Genetic assessment in familial PD |  |  |  |  |  |  |  |  |  |
| No. genetic mutations | 122 | 65.4 ± 3.0 | 14.2 ± 2.8 | 0 | – | 0.0 (0.0–2.1) | – | – | – |
| Genetic mutations | 20 | 65.1 ± 7.5 | 14.1 ± 2.6 | 6 | 10.1 ± 2.1 | 21.2 (7.8–45.6) | 4 | 37.4 ± 13.2 | 4 fatal |
| Type of genetic mutations |  |  |  |  |  |  |  | Range |  |
| GBA | 9 | 69.2 ± 4.8 | 13.9 ± 3.0 | 1 | 10.0 | 8.1 (0.2–44.5) | 0 | 18 | Recovery |
| SCNA (Park 4) | 5 | 51.2 ± 5.4 | 13.1 ± 2.5 | 0 | – | 0.0 (0.0–55.2) | – | – | – |
| Polg-1 (C128A>T, C2752>C) | 1 | 63.0 | 15.0 | 1 | 11.0 | 90.9 (2.3–413) | 1 (3) | 39–58 | Fatal |
| PINK-1 (D1S478) (Park 6) | 2 | 74.0 ± 1 | 16.5 ± 0.7 | 2 | 12.1 ± 0.9 | 82.6 (10.2–270) | 2 (3, 2) | 35–47 | 2 fatal |
| PINK-1 (D1S2674) (Park 6) | 1 | 64.0 | 14.2 | 1 | 10.0 | 100.0 (2.5–445) | 1 (2) | 18–25 | Recovery |
| LRRK2 (Gly2019Ser) (Park 8) | 2 | 74.5 ± 1 | 15.1 ± 2.8 | 1 | 10.9 | 33.3 (1.0–172) | 0 | 32 | Fatal |

AC, akinetic crisis; UPDRS, CI, conﬁdence interval; Uniﬁed Parkinson’s Disease Rating Scale part III; PY, person-year. The study was prospective; genetic identiﬁcations were obtained 3–13 years after disease onset.

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The precipitating event for AC were infections (pneumonia, gastroenteritis) in all episodes in the patient with POLG1 mutation, infections in three epi- sodes of patients with PINK1 mutations, surgical pro- cedure in one episode of a patient with PINK1 mutation, bone trauma with fracture in the patient with GBA mutation, and infection/gastroenteritis in the patient with LRRK2 mutation.

The precipitating event for PD patients who were non-carriers of genetic mutations were infections in 14 of 24, bone trauma/fracture in four of 24, surgical pro- cedure in one of 24, treatment withdrawal in two of 24, exposition to antidopaminergic drugs (clebopride in one, risperidone and amisulpride in two) in three.

The website material describes in detail each single genetically deﬁned case and two representative cases aﬀected by idiopathic PD.

# Discussion

AC is a relatively rare critical condition and only few studies could present data on more than 25 cases [1,5]. Although our cohort of patients was wide and intensively studied [15,16], oﬀering an outline of epidemiological distributions in an ethnically and phenomenologically homogeneous population, the rar- ity of the syndrome and the numerically modest results of genetic testing, probably due to underestimation of recessive and low penetrance mutations, resulted in a small number of patients, six patients aﬀected by AC out of 20 genetically identiﬁed parkinsonisms in a cohort of 756 patients followed for 10 years (Table 2). Therefore a possible criticism is that statistical infer- ences may be debatable. However, the striking coinci- dence of AC with the genetic diagnoses obtained in six patients indicates a disproportionate prevalence of this crisis in comparison with the population of PD patients. The incidence of AC in the described genetic mutation carriers (POLG1, PINK1, LRRK2, GBA) was a multiple (i.e. 21.2 vs. 3.0‰) of the known inci-

dence of AC in parkinsonian populations.

Moreover, AC episodes were recurrent in four out of the six patients, and all four were carriers of muta- tions involving mitochondrial functions: POLG1 (found in one of the four) is the gene that codes for the catalytic subunit of the mitochondrial DNA poly- merase; PINK1 (three patients) is the gene encoding a mitochondrial serine/threonine protein kinase. Three of the four patients died in the last crisis.

This ﬁnding suggests that mitochondrial dysfunc- tion may represent a predisposition to AC and to its possible lethal outcome. This assumption is challenged by the occurrence of AC in a carrier of LRRK2 muta- tion (with lethal outcome) and in a carrier of GBA

mutation, suggesting that mitochondrial dysfunction cannot be the only explanation.

LRRK2 is a member of the leucine-rich repeat kinase family involved in vesicular traﬃcking; expres- sion of LRRK2 mutants in diﬀerent experimental models increases the presence of autophagic compart- ments [17]. However, the pathogenic gain-of-function mutant form of LRRK2, G2019S, can cause defects in the morphology and dynamics (ﬁssion) of mitochon- dria [18].

Also in the GBA mutation (mostly leading to lyso- somal storage disorders), some recent evidence showed that mitochondria were dysfunctional and fragmented, with impaired respiration and reduced respiratory chain complex, including ATP synthase, activities [19]. Therefore the main conclusion is that our ﬁndings point to mitochondrial genetically driven dysfunc- tion as one of the most probable underlying causes of

AC.

It is suggested that in a cell environment where mitochondrial buﬀering power is defective, stressful conditions, such as the precipitating events described in our case cohort (infections, traumas etc.) could activate a stress cascade, altering the cellular energy state by inhibiting the electron transport chain. It is therefore suggested that the determinant factor in AC might be akin to inhibition of complex I activity, observed in brain mitochondria of rats exposed to neuroleptics [20] or in postmortem evaluations of patients aﬀected by neuroleptic malignant syndrome [21], which is a disorder similar to AC [4].

In order to conﬁrm/debate the hypothesis suggested by our preliminary ﬁndings, further studies will be needed, considering wider populations, assessing all cases of AC for genetic mutations and considering the risk of underestimation of genetic mutations because of reduced penetrance or recessive inheritance.

It is suggested that the construction of an observa- tional network might answer the question asked by our report, and might help further the search for the mechanism of AC and for its treatment.

# Disclosure of conflicts of interest

The authors declare no ﬁnancial or other conﬂicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Case descriptions of genetic and idiopathic parkisnonian patients experiencing AC.

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1. Onofrj M, Thomas A. Acute akinesia in Parkinson dis- ease. *Neurology* 2005; 64: 1162–1629.
2. Ueda M, Hamamoto M, Nagayama H, *et al.* Suscepti- bility to neuroleptic malignant syndrome in Parkinson’s disease. *Neurology* 1999; 52: 777–781.
3. Thomas A, Onofrj M. Akinetic crisis, acute akinesia, neuroleptic malignant-like syndrome, Parkinsonism- hyperpyrexia syndrome, and malignant syndrome are the same entity and are often independent of treatment withdrawal. *Mov Disord* 2005; 20: 1671; author reply

1671–1672.

1. Margeti'c B, Aukst-Margeti'c B. Neuroleptic malignant syndrome and its controversies. *Pharmacoepidemiol Drug Saf* 2010; 19: 429–435.
2. Takubo H, Harada T, Hashimoto T, *et al.* A collabora- tive study on the malignant syndrome in Parkinson’s disease and related disorders. *Parkinsonism Relat Disord* 2003; 9(Suppl. 1): S31–S41.
3. Albin RL, Dauer WT. Parkinson syndrome. Heteroge- neity of etiology; heterogeneity of pathogenesis? *Neurol- ogy* 2012; 79: 202–203.
4. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson’s disease: a clinic-pathological study of 100 cases. *J Neurol Neuro- surg Psychiatry* 1992; 55: 181–184.
5. Albanese A, Bonuccelli U, Brefel C, *et al.* Consensus statement on the role of acute dopaminergic challenge in Parkinson’s disease. *Mov Disord* 2001; 16: 197–201.
6. Invernizzi F, Varanese S, Thomas A, Carrara F, Onofrj M, Zeviani M. Two novel POLG1 mutations in a patient with progressive external ophthalmoplegia, levo- dopa-responsive pseudo-orthostatic tremor and parkin- sonism. *Neuromuscul Disord* 2008; 18: 460–464.
7. Singleton AB, Farrer M, Johnson J, *et al.* a-Synuclein locus triplication cause Parkinson’s disease. *Science* 2003; 302: 841.
8. Bonifati V, Roh'e CF, Breedveld GJ, *et al.* Early-onset parkinsonism associated with PINK1 mutations: fre- quency, genotypes, and phenotypes. *Neurology* 2005; 65: 87–95.
9. Valente EM, Abou-Sleiman PM, Caputo V, *et al.* Hereditary early-onset Parkinson’s disease caused by mutations in PINK1. *Science* 2004; 304: 1158–1160.
10. Funayama M, Hasegawa K, Kowa H, Saito M, Tsuji S, Obata F. A new locus for Parkinson’s disease (PARK8) maps to chromosome 12p11.2-q13.1. *Ann Neurol* 2002; 51: 296–301.
11. Neumann J, Bras J, Deas E, *et al.* Glucocerebrosidase mutations in clinical and pathologically proven Parkin- son’s disease. *Brain* 2009; 132: 1783–1794.
12. Onofrj M, Bonanni L, Manzoli L, Thomas A. Cohort study on somatoform disorders in Parkinson disease and dementia with Lewy bodies. *Neurology* 2010; 74: 1598–

1606.

1. Onofrj M, Varanese S, Bonanni L, *et al.* Cohort study of prevalence and phenomenology of tremor in dementia with Lewy bodies. *J Neurol* 2013; 260: 1731–1742.
2. Orenstein SJ, Kuo SH, Tasset I, *et al.* Interplay of LRRK2 with chaperone-mediated autophagy. *Nat Neu- rosci* 2013; 16: 394–406.
3. Niu J, Yu M, Wang C, Xu Z. Leucine-rich repeat kinase 2 disturbs mitochondrial dynamics via dynamin-like pro- tein. *J Neurochem* 2012; 122: 650–658.
4. Osellame LD, Rahim AA, Hargreaves IP, *et al.* Mito- chondria and quality control defects in a mouse model of Gaucher disease –links to Parkinson’s disease. *Cell Metab* 2013; 17: 941–953.
5. Burkhardt C, Kelly JP, Lim YH, *et al.* Neuroleptic med- ications inhibit complex I of the electron transport chain. *Ann Neurol* 1993; 33: 512–517.
6. Maurer I, Moller HJ. Inhibition of complex I by neuro- leptics in normal human brain cortex parallels the extra- pyramidal toxicity of neuroleptics. *Mol Cell Biochem* 1997; 174: 255–259.

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