MRI CNS Atrophy Pattern

Subjects: Neuroimaging
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MRI shows the three archetypal patterns of CNS volume loss underlying progressive ataxias in vivo, namely spinal atrophy (SA), cortical cerebellar atrophy (CCA) and olivopontocerebellar atrophy (OPCA). In line with the neuropathological discoveries of the XIX and XX centuries, MRI confirms today that there are three fundamental distribution patterns of CNS atrophy underlying progressive ataxias in vivo. They are SA, CCA and OPCA and can be inherited or acquired. Although the present trend driven by molecular genetics advances is to split progressive ataxias into hundreds of sometimes very rare conditions, a simple clumping of them according to the MRI-based CNS atrophy pattern is possible and might help diagnosis, possibly improve physiopathology understanding and may even cause future studies to rethink therapies for these uncommon but disabling diseases.

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1. Definite CNS Atrophy—Etiological Relationship

The SA pattern was exclusively observed in FRDA. The CCA pattern was observed in several acquired ataxias (alcoholic cerebellar degeneration, gluten ataxia, anti-glutamic acid decarboxylase ataxia, paraneoplastic cerebellar degeneration and sporadic adult-onset ataxia/idiopathic late-onset cerebellar ataxia), in many dominant ataxias (SCA5, SCA6, SCA8, SCA10, SCA11, SCA12, SCA13, SCA14, SCA15/16, SCA19/22, SCA20, SCA21, SCA26, SCA27, SCA28, SCA31, SCA35, SCA37, SCA38, SCA42, SCA43, SCA44, SCA47 and SCA48), all recessive ataxias with the exception of Boucher–Neuhauser Syndrome (BNS) and SCAR7 and in one X-linked ataxia (SCAX1).

The OPCA pattern was identified as MSA-C in a few dominant ataxias (SCA1-3, SCA7, SCA34, SCA36, DRPLA), two recessive ataxias (BNS and SCAR7) and the X-linked ataxia associated with the PRPS1 gene mutation.

2. Pontocerebellar Hypoplasia

MRI showed pontocerebellar hypoplasia in all three recessive diseases characterized by progressive ataxias and mental retardation with/out quadrupedal locomotion type 1–3 (CAMRQ1, CAMRQ2 and CAMRQ3). On the other hand, unfortunately, in some instances, the term “hypoplasia” was used to describe MRI findings of probable CAA as in SCAR25, SCAR28, SCAR31 and SCAX1.

3. Uncertain CNS Atrophy—Etiological Relationship

The CNS atrophy pattern was uncertain in 11 progressive ataxias. A small number of patients were examined with MRI in SCA40, SCA45, SCAR12 and SCAR15, and heterogeneous and non-specific MRI findings were observed or reported in SeSAME syndrome, spastic ataxia type 2 and spastic paraplegia 5A.

More articulated are the reasons for the inclusion of four further progressive ataxias in the category of uncertain CNS atrophy patterns, namely EOCA, AVED, SCAR27 and CANVAS. EOCA is recognized as a heterogeneous sporadic condition that was initially considered separated from FRDA. However, FRDA patients can present with an EOCA phenotype [1]. Initially, a CCA pattern was described in patients with EOCA, possibly contributing to the differentiation with FRDA [2]. However, subsequent reports described atrophy of the brainstem and spinal cord [3][4]. AVED is a recessive condition for which relatively few data on CNS morphology are available. No brain MRI abnormality was observed in some patients, whereas cerebellar atrophy was reported in others [5]. Moreover, in the only AVED patient examined with spinal MRI, no abnormality was found [6], but a decreased size of the upper cervical cord was apparent in a case shown by Heidelberg et al. [7]. Hence, despite the reasonable assumption of a SA pattern in AVED reflecting the sensory ataxia and the clinical similarity with FRDA [8][9], no definitive evidence of it has been provided so far. In the original description of SCAR27, a CCA pattern was recognized in two unrelated patients [10]. However, in a further patient, it was accompanied by atrophy of the pons and midbrain [11]. CANVAS is a recessive condition with marked clinical heterogeneity that has recently been recognized as responsible for apparently sporadic progressive ataxia [12][13][14][15]. CANVAS showed a pronounced heterogeneity concerning the distribution of the CNS atrophy in inherited progressive ataxia. In fact, the CCA pattern was observed in the majority of patients with CANVAS [16][17], but it was combined with atrophy in the spinal cord in some patients who were examined with cervical spine MRI [17], and also an OPCA pattern was reported in a few patients [13][14].

4. Progressive Ataxias Characterized by MRI Signal Changes

Some progressive ataxias are characterized by signal changes better demonstrated by T_2-weighted images, which, irrespective of the CNS atrophy severity and distribution patterns, can considerably help in identifying them. These include acquired and inherited causes. The signal changes in the acquired forms have been reviewed elsewhere [18][19][20]. The inherited forms include two dominant ataxias, namely ataxia-pancytopenia syndrome (OMIM 159550 [21], and SCA20 (OMIM 608687) [22], seven recessive ataxias, namely cerebrotendinous xanthomatosis (CTX) (OMIM 213700) [23], 2-hydroxic glutaric aciduria (OMIM 236792) [24], hypomyelinating leukodystrophy type 2 (HLD2) (OMIM 608804) [25], hypomyelinating leukodystrophy type 4 (OMIM 612233) [26], leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) (OMIM 611105)[27], leukoencephalopathy with ataxia (OMIM 615651) [28], sensory ataxic neuropathy, dysarthria and ophtalmoparesis (SANDO) (OMIM 607459) [29], SCAR4/SCA24 (OMIM 607317)[30] and the X-linked fragile-X tremor ataxia syndrome (FXTAS) (OMIM 300623) [31].

The signal in T_2-weighted images is symmetrically increased in the majority of these inherited ataxias, variably involving the cerebral WM, basal ganglia and thalami, cerebral peduncles, cerebellar peduncles, cerebellar WM, brainstem and spinal cord. The distribution is characteristic in HLD2 (OMIM 608804) [25], (LBSL) (OMIM 611105) [27], leukoencephalopathy with ataxia (OMIM 615651) [28], (SANDO) (OMIM 607459) [29], SCAR4/SCA24 (OMIM

607317)[30] and X-linked fragile-X tremor ataxia syndrome (FXTAS) (OMIM 300623) [31]. More distinctive is the symmetrically decreased signal in T2 or T2*-weighted images reflecting iron deposition in the surface of the brain in siderosis [18] and calcification of the dentate nuclei in SCA20 (OMIM 608687) [22].

5. Clinical, Diagnostic and Other Implications

As expected, the distribution of the loss of bulk matching one of the CNS atrophy patterns is in line with the constellation of clinical symptoms and signs in patients with progressive ataxias [32][33]. For instance, most of the so-called pure cerebellar dominant ataxias (ADCA type III) show a CCA pattern, whereas dominant ataxias with additional extra-cerebellar symptoms and signs (ADCA type I) show an OPCA pattern. FRDA, in which there is prominent sensory involvement, shows a SA pattern and spinal cord atrophy.

Overall, there is the relationship between the MRI CNS atrophy pattern and etiologies in progressive ataxias [34]. Changes with respect to the 2008 classification include the displacement of SCA13 from the OPCA to CCA pattern following the report by Subramony et al. [35] in a large family and three index cases, and displacement of SCA17 from CCA to a generalized CNS atrophy pattern.

Obviously, for diagnostic purposes, the relationship between the MRI CNS atrophy pattern and etiologies in progressive ataxias must be integrated with other clinical and laboratory data and, in the case of inherited progressive ataxias, with ethnicity and geographical distribution [8][36]. However, before this use for the diagnosis in a single patient, two notes of caution are worthy.

First, it is conceivable that in advanced stages of different ataxias, generalized atrophy of the CNS, including cerebellum, brainstem, spinal cord and cerebrum, takes place as a result of secondary axonal and trans-synaptic degeneration with the waning of differences between SA, CCA and OPCA patterns. This possibility is confirmed by the occurrence of cerebellar cortex atrophy in advanced cases of FRDA, the prototype of SA [37], atrophy of the spinal cord in SCA1 and SCA3 that are typical examples of OPCA [38][39], and of pontine atrophy in SCA13 and SCA36, two conditions characterized by CCA in the early phases [35][40][41]. In addition, the correlation in CANVAS between disease duration and MRI evidence of brainstem atrophy is in line with this hypothesis [14]. However, the proposed relationship is generally valid for the early and full clinical manifestation of diseases, and data in pre-symptomatic patients with dominantly transmitted ataxia show that early loss of bulk involves the cerebellum and pons in SCA1 and SCA2, two examples of OPCA pattern [42], but the cerebellum alone in SCA48 [43] that is an example of CCA.

Second, theoretically, in line with the known phenotype and genotype heterogeneity of inherited ataxias [8], it cannot be excluded that different CNS atrophy patterns can correspond to the same disease entity.

Beyond the diagnostic purpose, two additional potential consequences of awareness of the relationship between the three MRI-based CNS atrophy patterns and the etiologies of progressive ataxias can be envisioned. First, it may contribute to identifying shared cellular targets or metabolic pathways for diseases exhibiting the same

archetypal CNS atrophy pattern, thus improving the understanding of physiopathological mechanisms of progressive ataxias [8]. Second, from a therapeutic perspective, it may facilitate the repurposing of drugs or enlarge indications for inherited or acquired ataxia diseases sharing the same MRI atrophy distribution pattern (and similar distribution of neuronal systems damage) and corresponding patients [8], as was attempted in cases of CCA [44].

References

1. De Michele, G.; Filla, A. Other autosomal recessive and childhood ataxias. Handb. Clin. Neurol. 2012, 103, 343–357.
2. Klockgether, T.; Petersen, D.; Grodd, W.; Dichgans, J. Early onset cerebellar ataxia with retained tendon reflexes. Clinical, electrophysiological and MRI observations in comparison with Friedreich's ataxia. Brain 1991, 114, 1559–1573.
3. Ormerod, I.E.; Harding, A.E.; Miller, D.H.; Johnson, G.; MacManus, D.; du Boulay, E.P.; Kendall, B.E.; Moseley, I.F.; McDonald, W.I. Magnetic resonance imaging in degenerative ataxic disorders. J. Neurol. Neurosurg. Psychiatry 1994, 57, 51–57.
4. De Michele, G.; Di Salle, F.; Filla, A.; D'Alessio, A.; Ambrosio, G.; Viscardi, L.; Scala, R.; Campanella, G. Magnetic resonance imaging in "typical" and "late onset" Friedreich's disease and early onset cerebellar ataxia with retained tendon reflexes. Ital. J. Neurol. Sci. 1995, 16, 303–308.
5. Mariotti, C.; Gellera, C.; Rimoldi, M.; Mineri, R.; Uziel, G.; Zorzi, G.; Pareyson, D.; Piccolo, G.; Gambi, D.; Piacentini, S.; et al. Ataxia with isolated vitamin E deficiency: Neurological phenotype, clinical follow-up and novel mutations in TTPA gene in Italian families. Neurol. Sci. 2004, 25, 130–137.
6. El Euch-Fayache, G.; Bouhlal, Y.; Amouri, R.; Feki, M.; Hentati, F. Molecular, clinical and peripheral neuropathy study of Tunisian patients with ataxia with vitamin E deficiency. Brain 2014, 137, 402–410.
7. Heidelberg, D.; Ronsin, S.; Bonneville, F.; Hannoun, S.; Tilikete, C.; Cotton, F. Main inherited neurodegenerative cerebellar ataxias, how to recognize them using magnetic resonance imaging? J. Neuroradiol. 2018, 45, 265–275.
8. Beaudin, M.; Matilla-Dueñas, A.; Soong, B.-W.; Pedroso, J.L.; Barsottini, O.G.; Mitoma, H.; Tsuji, S.; Schmahmann, J.D.; Manto, M.; A Rouleau, G.; et al. The classification of autosomal recessive cerebellar ataxias: A consensus statement from the society for research on the cerebellum and ataxias task force. Cerebellum 2019, 18, 1098–1125.
9. Mascalchi, M.; Vella, A. Neuroimaging Applications in Chronic Ataxias. Int. Rev. Neurobiol. 2018, 143, 109–162.

10. Eidhof, I.; Baets, J.; Kamsteeg, E.-J.; Deconinck, T.; Van Ninhuijs, L.; Martin, J.-J.; Schüle, R.; Züchner, S.; De Jonghe, P.; Schenck, A.; et al. GDAP2 mutations implicate susceptibility to cellular stress in a new form of cerebellar ataxia. Brain 2018, 141, 2592–2604.
11. Breza, M.; Bourinaris, T.; Efthymiou, S.; Maroofian, R.; Athanasiou-Fragkouli, A.; Tzartos, J.; Velonakis, G.; Karavasilis, E.; Angelopoulou, G.; Kasselimis, D.; et al. A homozygous GDAP2 loss-of-function variant in a patient with adult-onset cerebellar ataxia. Brain 2020, 143, e49.
12. Montaut, S.; Diedhiou, N.; Fahrer, P.; Marelli, C.; Lhermitte, B.; Robelin, L.; Vincent, M.C.; Corti, L.; Taieb, G.; Gebus, O.; et al. Biallelic RFC1-expansion in a French multicentric sporadic ataxia cohort. J. Neurol. 2021, 268, 3337–3343.
13. Wan, L.; Chen, Z.; Wan, N.; Liu, M.; Xue, J.; Chen, H.; Zhang, Y.; Peng, Y.; Tang, Z.; Gong, Y.; et al. Biallelic Intronic AAGGG Expansion of RFC1 is Related to Multiple System Atrophy. Ann. Neurol. 2020, 88, 1132–1143.
14. Traschütz, A.; Cortese, A.; Reich, S.; Dominik, N.; Faber, J.; Jacobi, H.; Hartmann, A.M.; Rujescu, D.; Montaut, S.; Echaniz-Laguna, A.; et al. Natural History, Phenotypic Spectrum, and Discriminative Features of Multisystemic RFC1 Disease. Neurology 2021, 96, e1369–e1382.
15. Syriani, D.A.; Wong, D.; Andani, S.; De Gusmao, C.M.; Mao, Y.; Sanyoura, M.; Glotzer, G.; Lockhart, P.J.; Hassin-Baer, S.; Khurana, V.; et al. Prevalence of RFC1-mediated spinocerebellar ataxia in a North American ataxia cohort. Neurol. Genet. 2020, 6, e440.
16. Beecroft, S.J.; Cortese, A.; Sullivan, R.; Yau, W.Y.; Dyer, Z.; Wu, T.Y.; Mulroy, E.; Pelosi, L.; Rodrigues, M.; Taylor, R.; et al. A Māori specific RFC1 pathogenic repeat configuration in CANVAS, likely due to a founder allele. Brain 2020, 143, 2673–2680.
17. Cortese, A.; Tozza, S.; Yau, W.Y.; Rossi, S.; Beecroft, S.J.; Jaunmuktane, Z.; Dyer, Z.; Ravenscroft, G.; Lamont, P.J.; Mossman, S.; et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. Brain 2020, 143, 480–490.
18. Lieto, M.; Roca, A.; Santorelli, F.M.; Fico, T.; De Michele, G.; Bellofatto, M.; Saccà, F.; De Michele, G.; Filla, A. Degenerative and acquired sporadic adult onset ataxia. Neurol. Sci. 2019, 40, 1335–1342.
19. Hattingen, E.; Pilatus, U. (Eds.) Brain Tumor Imaging; Springer: Berlin/Heidelberg, Germany, 2016; ISSN 0942-3573.
20. Kumar, N.; Pandey, S.; Garg, R.K.; Holla, V.V. A case of subacute progressive cerebellar ataxia: Brownell-Oppenheimer variant of sporadic Creutzfeldt-Jakob disease. Neurol. India 2021, 69, 217–218.
21. Chen, D.-H.; Below, J.; Shimamura, A.; Keel, S.B.; Matsushita, M.; Wolff, J.; Sul, Y.; Bonkowski, E.; Castella, M.; Taniguchi, T.; et al. Ataxia-Pancytopenia Syndrome Is Caused by Missense Mutations in SAMD9L. Am. J. Hum. Genet. 2016, 98, 1146–1158.

22. Knight, M.A.; Gardner, R.J.M.; Bahlo, M.; Matsuura, T.; Dixon, J.A.; Forrest, S.M.; Storey, E. Dominantly inherited ataxia and dysphonia with dentate calcification: Spinocerebellar ataxia type 20. Brain 2004, 127, 1172–1181.
23. Dotti, M.T.; Federico, A.; Signorini, E.; Caputo, N.; Venturi, C.; Filosomi, G.; Guazzi, G.C. Cerebrotendinous xanthomatosis (van Bogaert-Scherer-Epstein disease): CT and MR findings. AJNR Am. J. Neuroradiol. 1994, 15, 1721–1726.
24. Seijo-Martínez, M.; Navarro, C.; Del Río, M.C.; Vila, O.; Puig, M.; Ribes, A.; Butron, M. L-2-hydroxyglutaric aciduria: Clinical, neuroimaging, and neuropathological findings. Arch. Neurol. 2005, 62, 666–670.
25. Biancheri, R.; Rosano, C.; Denegri, L.; Lamantea, E.; Pinto, F.; Lanza, F.; Severino, M.; Filocamo, M. Expanded spectrum of Pelizaeus-Merzbacher-like disease: Literature revision and description of a novel GJC2 mutation in an unusually severe form. Eur. J. Hum. Genet. 2013, 21, 34–39.
26. Magen, D.; Georgopoulos, C.; Bross, P.; Ang, D.; Segev, Y.; Goldsher, D.; Nemirovski, A.; Shahar, E.; Ravid, S.; Luder, A.; et al. Mitochondrial hsp60 chaperonopathy causes an autosomal-recessive neurodegenerative disorder linked to brain hypomyelination and leukodystrophy. Am. J. Hum. Genet. 2008, 83, 30–42.
27. van der Knaap, M.S.; Van Der Voorn, P.; Barkhof, F.; Van Coster, R.; Krägeloh-Mann, I.; Feigenbaum, A.; Blaser, S.; Vles, J.S.H.; Rieckmann, P.; Pouwels, P.J.W. A new leukoencephalopathy with brainstem and spinal cord involvement and high lactate. Ann. Neurol. 2003, 53, 252–258.
28. Depienne, C.; Bugiani, M.; Dupuits, C.; Galanaud, D.; Touitou, V.; Postma, N.; van Berkel, C.; Polder, E.; Tollard, E.; Darios, F.; et al. Brain white matter oedema due to ClC-2 chloride channel deficiency: An observational analytical study. Lancet Neurol. 2013, 12, 659–668.
29. Rantamaki, M.; Krahe, R.; Paetau, A.; Cormand, B.; Mononen, I.; Udd, B. Adult-onset autosomal recessive ataxia with thalamic lesions in a Finnish family. Neurology 2001, 57, 1043–1049.
30. Gauthier, J.; Meijer, I.A.; Lessel, D.; Mencacci, N.E.; Krainc, D.; Hempel, M.; Tsiakas, K.; Prokisch, H.; Rossignol, E.; Helm, M.H.; et al. Recessive mutations in VPS13D cause childhood onset movement disorders. Ann. Neurol. 2018, 83, 1089–1095.
31. Apartis, E.; Blancher, A.; Meissner, W.G.; Guyant-Maréchal, L.; Maltête, D.; De Broucker, T.; Legrand, A.-P.; Bouzenada, H.; Thanh, H.T.; Sallansonnet-Froment, M.; et al. FXTAS: New insights and the need for revised diagnostic criteria. Neurology 2012, 79, 1898–1907.
32. Rossi, M.; Anheim, M.; Durr, A.; Klein, C.; Koenig, M.; Synofzik, M.; Marras, C.; Van De Warrenburg, B.P.; on behalf of the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders. The genetic nomenclature of recessive cerebellar ataxias. Mov. Disord. 2018, 33, 1056–1076.

33. Sullivan, R.; Yau, W.Y.; O'Connor, E.; Houlden, H. Spinocerebellar ataxia: An update. J. Neurol. 2019, 266, 533–544.
34. Mascalchi, M. Spinocerebellar ataxias. Neurol. Sci. 2008, 29, 311–313.
35. Subramony, S.; Advincula, J.; Perlman, S.; Rosales, R.L.; Lee, L.V.; Ashizawa, T.; Waters, M.F. Comprehensive phenotype of the p.Arg420his allelic form of spinocerebellar ataxia type 13. Cerebellum 2013, 12, 932–936.
36. Klockgether, T. The clinical diagnosis of autosomal dominant spinocerebellar ataxias. Cerebellum 2008, 7, 101–105.
37. Harding, I.H.; Chopra, S.; Arrigoni, F.; Boesch, S.; Brunetti, A.; Cocozza, S.; Corben, L.A.; Deistung, A.; Delatycki, M.; Diciotti, S.; et al. Brain Structure and Degeneration Staging in Friedreich Ataxia: Magnetic Resonance Imaging Volumetrics from the ENIGMA-Ataxia Working Group. Ann. Neurol. 2021, 90, 570–583.
38. Martins, C.R., Jr.; Martinez, A.R.M.; De Rezende, T.J.R.; Branco, L.M.T.; Pedroso, J.L.; Barsottini, O.G.P.; Lopes-Cendes, I.; França, M.C. Spinal cord damage in Spinocerebellar Ataxia type 1. Cerebellum 2017, 16, 792–796.
39. Fahl, C.N.; Branco, L.M.T.; Bergo, F.P.G.; D'Abreu, A.; Lopes-Cendes, I.; França, M.C., Jr. Spinal cord damage in Machado-Joseph disease. Cerebellum 2015, 14, 128–132.
40. Ikeda, Y.; Ohta, Y.; Kobayashi, H.; Okamoto, M.; Takamatsu, K.; Ota, T.; Manabe, Y.; Okamoto, K.; Koizumi, A.; Abe, K. Clinical features of SCA36: A novel spinocerebellar ataxia with motor neuron involvement (Asidan). Neurology 2012, 79, 333–341.
41. Herman-Bert, A.; Stevanin, G.; Netter, J.-C.; Rascol, O.; Brassat, D.; Calvas, P.; Camuzat, A.; Yuan, Q.-P.; Schalling, M.; Dürr, A.; et al. Mapping of spinocerebellar ataxia 13 to chromosome 19q13.3-q13.4 in a family with autosomal dominant cerebellar ataxia and mental retardation. Am. J. Hum. Genet. 2000, 67, 229–235.
42. Jacobi, H.; Reetz, K.; du Montcel, S.T.; Bauer, P.; Mariotti, C.; Nanetti, L.; Rakowicz, M.; Sulek, A.; Durr, A.; Charles, P.; et al. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: Analysis of baseline data. Lancet Neurol. 2013, 12, 650–658.
43. Genis, D.; Ortega-Cubero, S.; Nicolás, H.S.; Corral, J.; Gardenyes, J.; de Jorge, L.; López, E.; Campos, B.; Lorenzo, E.; Tonda, R.; et al. Heterozygous STUB1 mutation causes familial ataxia with cognitive affective syndrome (SCA48). Neurology 2018, 91, e1988–e1998.
44. Kimura, N.; Kumamoto, T.; Masuda, T.; Nomura, Y.; Hanaoka, T.; Hazama, Y.; Okazaki, T.; Arakawa, R. Evaluation of the effect of thyrotropin releasing hormone (TRH) on regional cerebral blood flow in spinocerebellar degeneration using 3DSRT. J. Neurol. Sci. 2009, 281, 93–98.