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ORIGINAL ARTICLE

Rett syndrome and the role of national parent associations within a European context

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Abstract

Rett syndrome (RTT) is a rare neurodevelopmental disorder arising from a genetic mutation on the X chromosome. In recent years there has been an increasing focus in Europe on developing links, both within and between countries, between researchers, clinicians, therapists, individuals with RTT and their families or caregivers in order to maximise approaches towards treatment and long-term-management of the disorder. This paper seeks to place RTT, especially the support of families living with RTT, in a European context. It explores the important role played by both the national Rett parent associations and the Rett expertise centres that exist in many of the Member States of the European Union and places the contribution of both within the context of European policy on rare diseases.

Key words

Rett syndrome, parent associations, centres of expertise, European Union, European policy, rare diseases, rare disease registries.

Introduction

Rett syndrome (RTT) is a rare neurodevelopmental disorder thought to affect 1 in 9,000-15,000 live female births [1-4]. This is due to a genetic mutation on the X chromosome which is most commonly found in the MECP2 gene [5-8] although other variants have been identified. The severity of the clinical presentation varies according to the specific mutation [9-14]. Typically, however, the syndrome is characterised by seemingly-normal development in the early months of life following which there is a noticeable regression of skills, beginning between 6 and 18 months of age [15]. A cascade of evolving clinical features has been delineated according to a series of stages [16, 17]. Individuals with RTT demonstrate a loss of motor and communication skills [18, 19], in large part due to the influence of dyspraxia which affects their ability to make purposeful movements; additional concomitant features generally include severe breathing abnormalities, epilepsy and scoliosis [20]. It is a severe, lifelong disorder which impacts greatly on quality of life and leads to a shortened life expectancy [21-24].

In 2007 Bird and colleagues first demonstrated that the symptoms of RTT could be reversed in mice [25]. Since then much research has been devoted to both the treatment and potential cure of RTT [26-29] as well as the development of more functional therapies which seek to enhance the participation and quality of life of individuals living with this rare disorder [30-37].

Both the literature and the number of clinicians worldwide with specialist knowledge and skills relating to this population are small but increasing, as is the number of multidisciplinary centres specialising in the care and management of individuals with RTT and their families. At the present time, however, there is huge variability in knowledge and expertise between countries and huge variability in clinical practices both between and within countries. There are few national and no internationally-agreed models for the delivery of clinical services to this population; neither are there international guidelines for the overall clinical management of the syndrome although these have been proposed for individual aspects, such as scoliosis [38] and growth and nutrition [39].

Within this global context, there is a growing recognition of the need to strengthen collaborations within and between professional and parent groups at both European and international levels, and it is clear that Rett parent associations can provide a valuable role in disseminating and sharing information and training, and in supporting both families and professionals. Rett Syndrome Europe (RSE, http://www.rettsyndrome.eu/association-rse/europe/) has formed as an umbrella organisation for the European parent associations and, as a member of EURORDIS (the European Rare Diseases Organisation, http://www.eurordis.org/), also makes a vital contribution to the debate on European policy in relation to rare diseases. Likewise, in recent years, professionals (researchers, clinicians and therapists) from a number of expert centres across Europe have come together to form ESRRA, the European Scientific Rett Research Association (http://www.europeanscientificrettresearchassociation.eu/), a collaborative European platform for research focusing on RTT. Beyond Europe, international organisations such as rettsyndrome.org (https://www.rettsyndrome.org/) similarly give invaluable impetus to harnessing and stimulating developments in knowledge and expertise and promoting a sense of community between families and professionals within this relatively small field.

This paper offers an overview of the situation relating to RTT in countries within the European Union (EU) and European Economic Area (EEA) as of 2015.

European Rett syndrome conferences

In 2009 the first European Rett Syndrome Congress was held in Milan, Italy. This was an important milestone in bringing together researchers, scientists, educators, therapists and families to explore aspects relating to then-current research and treatment of RTT. The value of such a pan-European format was recognised and a second European conference followed in Edinburgh in 2010. In 2013 this model was again repeated with the third European Rett Syndrome Conference (ERSCM2013). Entitled 'Research Update and Preventive Management', this three-day conference was held in Maastricht, The Netherlands, and attracted 340 participants from 31 countries, representing 19 Member States of the EU, two EEA States, and ten other countries. The wishes and needs of parents, as expressed by the Rett parent associations and Rett syndrome foundations, were central to the development of the programme. The conference proved to be an exciting and stimulating opportunity for the sharing and dissemination of information concerning the latest developments in scientific and medical research and therapies, with separate seminar streams offered for researchers and scientists and for therapists and families, in addition to shared sessions open to all.

During the 'parent track' there was a particular emphasis on fostering opportunities for networking and information exchange between the national Rett parent associations; sessions at both the beginning and end of the conference were devoted to the European parent associations sharing information on their countries whilst RSE also held its annual General Assembly during the conference. At the close of the conference the organising committee and RSE signed a joint statement declaring their support for the European Union policy on rare diseases and defining more precisely the wishes of the European parent organisations in relation to the care and cure of RTT.

Of the 21 EU and EEA Member States present at the conference, 18 parent associations offered a presentation during the conference. In addition, presentations were given by the Israeli and Russian Rett parent associations. Each country was asked to set the scene by providing some basic national population statistics as well as statistics for RTT in that country, as far as available. Information on any Rett expertise centres or specialists in the field, together with an outline of the aims, activities and wishes of the parent association and/or foundation (if one existed) was also requested. The slides from these presentations can be accessed through the website of the Dutch Rett parent association (NRSV, http://www.rett.nl/).

Key information relating to the Rett parent associations in the EU and EEA Member States is shown in Table 1, whilst Table 2 provides an overview of centres of expertise and/or main hospitals providing diagnosis and medical care/advice and/or conducting research into RTT. The information contained within the tables is as presented by the national parent associations during ERSCM2013, supplemented by information taken from the websites of the national parent associations and/or email contact with parent representatives/medical consultants from each of the countries (up to September 2015). Additional and/or updated information on the current situation in each country (including details of parent association activities) can be accessed via the website addresses listed in the tables.

The fourth European Congress on Rett Syndrome took place in Rome, Italy, during the last weekend of October, 2015.

Comparisons across Europe

As of 2015 between five and ten European countries have (to varying degrees) either a national Rett expertise centre or specialised multidisciplinary Rett clinics, some of which are embedded within centres for rare diseases. A number of experts and researchers from these centres collaborate through ESRRA, as described above. Several countries have one or more hospitals providing a diagnostic service and/or one or more medical experts offering advice and clinical management of the syndrome, whilst other European countries have no experts in RTT and rely on services aimed at general disabilities (for further details see Table 2). In these cases the role of the national parent association, where one exists, is especially crucial in supporting families and professionals alike.

Table 1. EU & EEA Member States information: national population and Rett statistics (known and estimated), and parent association details

Country[a]	Population[b]	Birth rate per 1,000 population[b]	Estimated number of girls born per year with RTT[c]	Number of families/individuals known to have RTT (approximate in some cases)[d,e]	Parent association name & website
Austria	8.22 million	8.76	2.3-3.9	102[d]	*Österreichische Rett-Syndrom Gesellschaft (ÖRSG)* Founded 1996 www.rett-syndrom.at Member of *Pro-Rare Austria*
Belgium	10.45 million	9.99	3.4-5.7	80[d]	*Belgische Rett Syndroom Vereniging (BRSV)* Founded 1988 www.rettsyndrome.be
Bulgaria	6.92 million	8.92	2.0 -3.3	No information available	No Rett parent association registered with *RSE*
Croatia	4.47 million	9.49	1.4-2.3	29[e]	No Rett parent association registered with *RSE*
Cyprus	1.17 million (Republic & Northern Cyprus)	11.44	0.4-0.7	Several[d] (clinical rather than molecular diagnosis)	No Rett parent association registered with *RSE* *Pancyprian Association for Rare Genetic Disorders ('Unique Smiles')* offers support to families via Facebook
Czech Republic	10.63 million	9.79	3.4-5.6	50[d] (unofficial)	*Rett Community Association* Founded 2004 www.rett-cz.com/cz Member of *CAVO, Czech Association of Rare Diseases*
Denmark	5.57 million	10.22	1.8-3.1	123[d]	*Landsforeningen Rett Syndrom* Founded 1988 www.rett.dk Member of *Rare Diseases Denmark*
Estonia	1.26 million	10.29	0.4-0.7	No information available	No Rett parent association registered with *RSE*
Finland	5.27 million	10.35	1.8-3.0	60[d] (unofficial)	*Rett ry – Rett Finland* (formerly *Autistien ja Rett-henkiloiden Tuki ry, AURE ry*) Founded 1989 www.aure.fi
France	66.26 million	12.49	26.9-44.9	523[d]	*Association Française du Syndrome de Rett (AFSR)* Founded 1988 https://afsr.fr
Germany	82 million	8.42	22.1-36.8	623[d]	*Elternhilfe für Kinder mit Rett-Syndrom in Deutschland e.V.* Founded 1987 www.rett.de
Greece	11 million	8.8	3.1-5.1	No information available	*Άγγελοι γης ('Angels on Earth')* Founded 2011 www.rettgreece.gr Member of *Panhellenic Association of Rare Diseases*
Hungary	9.92 million	9.26	3.0-5.0	80[d]	*Magyar Rett Szindróma Alapítvány* Founded 1995 www.rettszindroma.hu Member of *RIROSZ, National Association of Rare Diseases*
Iceland	317,350	13.09	0.14-0.23	2[d] (verified through DNA analysis)	*Gudrun's Rett Syndrome Research Trust* Founded 2012 http://rettenglar.yolasite.com
Ireland	4.83 million	15.18	2.5-4.1	No information available	*The Rett Syndrome Association of Ireland* Founded 2003 http://rettsyndrome.ie
Italy	61.68 million	8.84	17.7-29.4	660[e]	*Associazione Italiana Rett (AIRETT)* Founded 1990 www.airett.it
Latvia	2.17 million	9.79	0.7-1.2	No information available	No Rett parent association registered with *RSE*
Lithuania	3.51 million	9.36	1.1-1.8	No information available	No Rett parent association registered with *RSE* *Lietuvos autizmo asociacija "Lietaus vaikai"(Lithuania Autism Association)* offers support to families Founded 2013 www.lietausvaikai.lt

(Continues)

Table 1. *(Continued)*

Country[a]	Population[b]	Birth rate per 1,000 population[b]	Estimated number of girls born per year with RTT[c]	Number of families/individuals known to have RTT (approximate in some cases)[d,e]	Parent association name & website
Luxembourg	521,000	11.75	0.2-0.3	No information available	No Rett parent association registered with *RSE* *Autisme Luxembourg asbl* offers support to families Founded 1981 http://www.autisme.lu *ALAN – Rare Diseases Luxembourg* also supports families Founded 1998, rare disease included from 2005 http://www.alan.lu
Malta	412,655	10.24	0.1-0.2	4[d]	No Rett parent association registered with *RSE*
Netherlands	16.88 million	10.83	5.9-9.9	175[d]	*Nederlands Rett Syndroom Vereniging (NRSV)* Founded 2008 www.rett.nl *Stichting Terre - Dutch Rett Syndrome Foundation* Founded 2008 www.stichtingterre.nl
Norway	5.15 million	12.09	2.01-3.36	130[d]	*Norsk Forening for Rett Syndrom* Founded 1987 www.rettsyndrom.no
Poland	38.35 million	9.77	12.1-20.2	70[d]	*Ogólnopolskie Stowarzyszenie Pomocy Osobom Z Zespołem Retta (OSPOzZR)* Founded 1997 http://rettsyndrome.pl
Portugal	10.81 million	9.42	3.3-5.5	No information available	*Associação Nacional de Pais e Amigos Rett (ANPAR)* Founded 2002 http://anpar.planetaclix.pt
Romania	21.73 million	9.27	6.5-10.9	16[e]	*Asociatia "Un inger pentru ingeri" ('An angel for the angels')* Founded 2013 www.asociatiauningerpentruingeri.ro
Slovakia	5.44 million	10.01	1.8-2.9	30[d]	*Rett Slovakia (Nadacia pre pomoc l'ud'om postihnutým Rettovym syndrómom-Slovensko)* Founded 2002 No website
Slovenia	1.99 million	8.54	0.6-0.9	No information available	*Tihi angeli ('Quiet angels')* - not currently active
Spain	47.74 million	9.88	15.2- 25.3	426[e]	*Asociación Española de Síndrome de Rett* Founded 1992 www.rett.es *Asociación Catalana del Síndrome de Rett* www.rettcatalana.es Members of the *Spanish Federation of Rare Diseases*
Sweden	9.72 million	11.92	3.8-6.3	250[d]	*Rett syndrome I Sverige (RSIS)* Founded 1997 www.rsis.se
UK	63.74 million	12.22	25.3-42.2	255[e]	*Rett UK* Founded 1985 http://www.rettuk.org Member of *Rett Disorders Alliance of the UK* Founded 2015 Includes: *Rett UK, Reverse Rett, Cure Rett, Reverse MECP2, FOXG1 UK, CDKL5 UK, Rett Education UK*

Additional information on each country (including details of parent association activities) can be accessed via the parent association websites as listed in this table or via the website of *Rett Syndrome Europe* (http://www.rettsyndrome.eu/association-rse/europe/). In addition, the slides which were presented by national parent associations during the 'Country Updates' sessions of ERSCM2013 can be accessed via: http://www.rett.nl

[a]Countries are arranged in alphabetical order. Liechtenstein is not included.

[b]Country population as of mid-2014, annual crude birth rate, and sex ratio at birth are all taken from: http://www.indexmundi.com/europe.html.

[c]Adjusted per country according to sex ratio at birth (varying between 1.04-1.07 male(s)/female) and calculated to show upper and lower potential limits taking into account an estimated incidence of Rett syndrome as 1 per 9,000-15,000 live female births.

[d]Numbers of 'known' individuals/families as reported by the national parent associations.

[e]Numbers of individuals registered on the Rett Database Network as of September 2015 (shown where numbers of 'known' individuals were not available through the parent association), see: https://www.rettdatabasenetwork.org/.

Table 2. Overview of centres of expertise and hospitals providing diagnosis, medical care and advice for Rett syndrome in EU & EEA Member States

Country[a]	Overview of experts and/or expertise centres
Austria	Expertise centre for RTT: under development Diagnosis and medical care/advice: Departments of Medical Genetics and Paediatric and Adolescent Neurology, Medical University of Vienna, in cooperation with other specialists/clinics Research: Medical University of Graz
Belgium	Diagnosis, medical care/advice: Centre for Developmental Disabilities, University Hospital, Leuven follows up all rare diseases and disorders with developmental delay, other University Hospitals across Belgium offer support for epilepsy, scoliosis, nutrition Second opinions/medical care/advice: Rett Expertise Centre Maastricht (Netherlands) may be consulted
Bulgaria	Diagnosis, medical care/advice: Paediatric Neurology Clinic of St Nahum Hospital in Sofia
Croatia	Diagnosis – Institute Rudjer Boskovic and the Children's Hospital Zagreb Medical care/advice – Centre of Expertise for Congenital Disorders at the Children's Hospital, Zagreb, and Neuropaediatric Departments of the Clinical Hospitals in Zagreb, Split, Osijek and Rijeka
Cyprus	Diagnosis, medical care/advice, research – Makarios Children's Hospital and Cyprus Institute of Neurology and Genetics
Czech Republic	Diagnosis, medical/paramedical care and advice – University Hospital of Motol, Prague A few schools/day care centres offer education and consultancy specific to RTT
Denmark	Expertise centre for RTT – Danish Centre for Rett Syndrome (part of the Kennedy Centre at Glostrup) http://www.kennedy.dk Diagnosis, medical/paramedical care, advice, research – multidisciplinary team in Glostrup, in cooperation with local hospitals
Estonia	Diagnosis and medical care/advice – consultant at Tartu University Hospital, Children's Clinic
Finland	Diagnosis - Child neurology departments at university hospitals across Finland (rare disease expertise centres will be established at all university hospitals, currently available at Helsinki University Central Hospital and in Turku) Medical care/advice – child neurologist with a special interest in RTT at Children's Hospital of Helsinki, basic health care provided by hospitals across Finland, Government-funded therapy provided weekly according to each individual's personal rehabilitation plan
France	Expertise centre for RTT – due to open at Necker Enfants Malades in Paris in 2015 Diagnosis, medical/paramedical care, advice, research – a range of experts/teams at various hospitals across France, e.g. hospitals in Paris, Marseille, Douai, Nancy, Tours, Barr, Bordeaux, Dijon
Germany	Diagnosis, medical care/advice – clinics in Kassel, Göttingen and Langen-Depstedt
Greece	Diagnosis, medical care/advice – several doctors across Greece have an interest in RTT
Hungary	Diagnosis and research – Rett Centre/Medical Genetics, University of Pécs *PART* and *DROP* programmes for families (therapy and education) and professionals (professional development/training) arranged by parent association
Iceland	Expertise centre for RTT – State Diagnostic and Counselling Centre (SDCC) http://www.greining.is Diagnosis, medical care/advice – collaboration between SDCC, neurology department of the Children's Hospital, and Benefit Society for Children with Disabilities
Ireland	Diagnosis – National Centre for Medical Genetics, Dublin Medical care and advice – hospitals across Ireland offer general support, some families seek more specific assessment and advice from UK Rett clinics
Italy	Expertise centres for RTT – Genoa, Milan, Rome, Siena, Messina Diagnosis, medical care/advice, research – range of consultants and researchers at centres in Genoa, Milan, Rome, Siena, Messina Founding member of ESRRA
Latvia	Diagnosis, medical care/advice – Children's Clinical University Hospital, Riga is the only hospital in Latvia that offers specialised multi-disciplinary treatment and care for rare diseases, the Medical Genetics Department provides genetic testing and counselling across all ages
Lithuania	Diagnosis – Coordinating Centre for Rare Paediatric Diseases, Children's Hospital Vilnius Medical care and advice – Child Development Centre, Vilnius and hospitals across Lithuania offer general support
Luxembourg	Diagnosis, medical care and advice – neurologist at Centre Hospitalier de Luxembourg, supported by experts in neighbouring countries e.g. Rett Expertise Centre Maastricht (Netherlands), CHU de Liège (Belgium)
Malta	Diagnosis, medical care/advice – included within Malta's National Care for Disabled Persons (KNPD) Education/therapy – *INSPIRE* Foundation offers holistic programmes and services to children and adults with various disabilities http://inspire.org.mt
Netherlands	Expertise centre for RTT – Rett Expertise Centre Maastricht, national reference centre recognised by the Dutch government http://gkc.daily-cms.com/pages/Rett_syndroom Diagnosis, medical care/advice, research – multidisciplinary team in Maastricht in cooperation with other (University) Hospitals and local teams Founding member of ESRRA

(Continues)

Table 2. *(Continued)*

Country[a]	Overview of experts and/or expertise centres
Norway	Expertise centre for RTT – Frambu Resource Centre for Rare Disorders (national resource centre for people with rare disorders and disabilities) http://www.frambu.no/retts-syndrom Diagnosis, medical care/advice and research – multidisciplinary team at Frambu
Poland	Diagnosis – Medical Universities in Bialystok, Warsaw, Krakow Medical care/advice – provided by centres for general disabilities (e.g. cerebral palsy, autism) with a (small) number of medical specialists who have an interest in RTT based in University Medical Centres across Poland
Portugal	Diagnosis, medical care/advice – Paediatric neurology departments of Hospital de Santo Antonio, Porto (also provides second opinions) and hospitals in Coimbra and Lisbon
Romania	Diagnosis – Carol Davila University of Medicine, Bucharest or hospitals in other countries e.g. Bulgaria, Hungary, Spain Medical care/advice – Paediatric Neurology Department of Carol Davila University manages seizures, hyperventilation problems, kinetic and psychotherapy programmes, other hospitals across Romania offer general support
Slovakia	Diagnosis – Comenius University Hospital in Bratislava or via University Hospital of Motol, Prague (Czech Republic) Medical care/advice – hospitals across Slovakia offer general support
Slovenia	Diagnosis, medical care/advice – Department of Child, Adolescent and Developmental Neurology, University Children's Hospital, Ljubljana sees all cases of RTT and organises further therapies through local hospitals/teams
Spain	Expert centre for RTT – Hospital Sant Joan de Deu in Barcelona Diagnosis, medical care/advice and research – child neurologists and local teams at hospitals across Spain, in cooperation with Sant Joan de Deu
Sweden	Expertise centre for RTT – Swedish Rett Centre in Östersund www.rettcenter.se Diagnosis, medical care/advice and research – multidisciplinary team at Östersund, in cooperation with other hospitals/local teams Founding member of ESRRA See also – Ågrenska, National Competence Centre for Rare Diseases http://www.agrenska.se
UK	Expertise centres for RTT: under development Diagnosis, medical care/advice and research – specialist multidisciplinary RTT clinics in London, Manchester, Nottingham and Cardiff, in cooperation with local hospitals/teams Founding member of ESRRA

The information presented in this table is as reported by the national parent associations during ERSCM2013, with additional information taken from the websites of the national parent associations and/or representatives from the countries (as of September 2015). Further updates on the current situation in each country can be accessed through the website of the relevant parent association (addresses shown in Table 1), any of the websites listed in this table, or the website of *Rett Syndrome Europe* (http://www.rettsyndrome.eu/association-rse/europe/).

[a]Countries are arranged in alphabetical order. Liechtenstein is not included.

All of the European parent associations listed in Table 1 exist to offer support and networking opportunities for families of individuals with RTT. They also see that they have an important role in disseminating information and raising awareness of RTT, both in keeping families up to date with new advances in research and in increasing the knowledge of professionals in their countries. The majority of associations are volunteer-led by parents and other family members; a few of the larger organisations are able to fund administrative and, occasionally, support staff to bolster and extend the work of the parents. In some cases, they are also in a position to fund research or even to support centres of expertise with funding. All but one of the existing parent associations host websites as a medium for sharing information and most use social media such as Facebook as a support mechanism.

Furthermore, a number of countries benefit from Rett foundations or research trusts which may exist in place of or in addition to the national parent association. The focus of such organisations is to raise funds for and to promote basic and applied research in relation to the treatment and cure of RTT. For example: in the Netherlands, the Stichting Terre-Dutch Rett Syndrome Foundation and in Iceland, Gudrun's Rett Syndrome Research Trust, whilst in the UK, the Rett Disorders Alliance of the UK was formed in July 2015, a collaboration of organisations working with and for the benefit of RTT and RTT-like disorders. This alliance comprises: Rett UK, Reverse Rett, Cure Rett, Reverse MECP2, FOXG1 UK, CDKL5 UK, and Rett Education UK. International collaborations are also evident. For example, Reverse Rett (formerly Rett Syndrome Research Trust UK) works in partnership with the US-based Rett Syndrome Research Trust and Cure Rett is in partnership with rettsyndrome.org in the US.

Databases and registries

Several European countries have some form of national database or registry specifically for RTT, for example, France, Italy, Portugal, Spain, UK[1]. These and others also contribute to larg-

[1]Some of these registries are listed on Orphanet: http://www.orpha.net/consor/cgi-bin/ResearchTrials_RegistriesMaterials.php?lng=EN&type_list=researchtrials_search_simple_shd&data_id=91&Disease(s)/group%20of%20diseases=Rett-syndrome&search=ResearchTrials_RegistriesMaterials_

er European or international RTT databases, for example, the Rett Database Network (https://www.rettdatabasenetwork.org) and/or InterRett (http://www.aussierett.org.au/). As of September 2015, the Rett Database Network held information on just over 2,000 individuals from 14 countries across Europe and further afield.

In addition, a number of mutation databases exist, which, in the era of 'next generation sequencing' (NGS) [40] are invaluable in contributing to an understanding of the biology associated with rare diseases such as RTT [41]. One such database to which a number of European (and other) countries contribute is RettBase, a MECP2 variation database, initiated by John Christodoulou and colleagues (http://mecp2.chw.edu.au/) [42]. Recently, information from this database has been incorporated into LOVD 3.0 (Leiden (open) Source Variation Database, http://www.lovd.nl/3.0/home) [43], a locus-specific database which seeks to connect NGS-driven collections built upon whole exome - and whole genome sequencing, such as ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/) and EVS (http://evs.gs.washington.edu/EVS/), and global initiatives such as the Global Alliance for Genomics and Health (http://genomicsandhealth.org).

LOVD's capability to include phenotypic HPO-based information is also considered to be one of its strengths (http://human-phenotype-ontology.github.io/about.html).

Wishes and future aims of the European parent associations

In general terms, all parent associations express a wish for early diagnosis and better medical, therapeutic and care services, increased support for families and increased dissemination and application of evidence-based knowledge in order to improve quality of life for individuals with RTT and their families. All families ultimately hope for a 'cure' for RTT.

In more specific terms, they call for further research and funding for research into areas such as epilepsy, scoliosis, brainstem dysfunction, genetics and stem cell research. Several associations hope for increased recognition of the syndrome within the health insurance system and for increased funding to enable the buying or renting/loan of medical equipment and communication aids. There is also a desire expressed by all associations for collaboration with and between scientific researchers, increased contact and networking between national parent associations, collaboration between Rett expertise centres in different countries and the establishment of national centres of expertise in countries where they do not currently exist. Furthermore, they advocate for the building up of pan-European specialist networks, linking medical experts and therapists within and between countries and facilitating the training and recruiting of specialists in countries where they are currently lacking.

European policy on rare diseases

Of particular relevance at the time of ERSCM2013 were the provisions for the creation of 'European reference networks' (ERNs) written into Articles 12 and 13 of the 2011 Cross-Border Healthcare Directive (Directive 2011/24/EU)[2], which built on earlier recommendations made by the Council of the European Union for Member States to develop their own national plans for rare diseases[3]. Quality criteria for 'Centres of Expertise for Rare Diseases' were also provided by the European Union Committee of Experts on Rare Diseases (EUCERD) in 2011[4], following which core indicators for the aforementioned national plans/strategies[5] and further recommendations for RD patient registration and data collection[6] and for Rare Disease ERNs[7] were released by EUCERD in 2013. Included in these recommendations was recognition of the integral role of patient/parent organisations.

It was in support of these policy developments, as well as to convey the more specific wishes of the Rett parent associations as outlined above, that the joint statement aimed at the Directorate General for Health and Consumers Affairs of the European Commission was signed at the end of the third European Rett Syndrome Conference in October 2013.

Following publication of the European Commission's Delegated Decision (2014/286/EU)[8] and Implementing Decision (2014/287/EU)[9] in March 2014, further clarification on the structure of RD ERNs was provided through a EUCERD joint action workshop set up to review progress in Member States in October 2014[10]. During this meeting, the suggested grouping of rare diseases within the new structure of ERNs was first promulgated and in June 2015 the final decision of the EC Expert Group on Rare Diseases[11]

Simple&ChdId=91&lng=EN&ResearchTrials_ResearchTrials_RegistriesMaterials_diseaseGroup=rett-syndrome&ResearchTrials_ResearchTrials_RegistriesMaterials_diseaseType=Pat&ResearchTrials_ResearchTrials_RegistriesMaterials_RegCategory=NN&ResearchTrials_ResearchTrials_RegistriesMaterials_country=NN&ResearchTrials_ResearchTrials_RegistriesMaterials_GeographicType=null&ResearchType=Reg

[2]See http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:en:PDF

[3]Council Recommendation of June 8, 2009, on an action in the field of rare diseases (2009/C 151/02).

[4]See http://www.EUCERD.eu/upload/file/EUCERDRecommendationCE.pdf.

[5]See http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf

[6]See http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

[7]See http://www.eucerd.eu/?post_type=document&p=2207

[8]See http://ec.europa.eu/health/ern/docs/ern_delegateddecision_20140310_en.pdf

[9]See http://ec.europa.eu/health/ern/docs/ern_implementingdecision_20140310_en.pdf

[10]See http://www.eucerd.eu/wp-content/uploads//2015/02/WP8Workshop_ERN_2014.pdf

[11]EUCERD's mandate ended in July 2013 and was replaced from 2014 by the EC

regarding "the grouping of RD into thematic networks and the necessity of a patient-centred approach to RD ERNs" (*Addendum*, p. 2) was published as an Addendum[12] to the EUCERD Recommendations of January 2013. According to these groupings RTT would most naturally seem to sit within an ERN for 'Rare neurological diseases' (*Addendum*, p. 8). A further account of recent developments in European policy and their implications for RTT can be found in Townend et al, 2015 [40] whilst a commentary on the challenges and opportunities to be offered by the development of ERNs can be found in Morciano et al, 2015 [44].

Discussion

The European Commission's policy on rare diseases provides significant political leverage within the Member States of the EU in the quest to raise awareness, to promote research and develop a stronger knowledge base, and to provide more equitable, higher quality services and support for individuals and families affected by rare disorders like RTT. On its own it is unlikely that any rare disorder would be high on the agenda of a national government. The European Commission's inclusion of rare diseases within Articles 12 and 13 of the Cross-Border Directive and the subsequent recommendations of EUCERD are, however, clear signals that minority health groups cannot and should not be ignored. Furthermore, pan-European collaboration between stakeholders – parents, professionals (clinicians, therapists, educators), researchers – is recognised as an integral and fundamental requirement. Within this context umbrella organisations such as ESRRA, as a collaboration of professionals and researchers, and RSE, as a collaboration of parents associations, have important roles to play whilst European (as well as international) conferences offer valuable opportunities for these groups to come together to engage in discussion and dissemination of latest research, treatment and management techniques. A commitment by all EU countries to the sharing of clinical data through pan-European (and/or international) registries/databases for rare diseases such as RTT is also a vital step in the collaborative endeavour.

There have been a number of attempts to construct (genetic) databases in relation to RTT, at country-based, European and international levels [42-43, 45-47]. Where these do exist they prove valuable sources of data for research purposes [21, 23, 24, 48-50]. At present, however, most countries are unable to report definitive figures for numbers of individuals diagnosed with RTT in their country. In part this is due to the fact that some individuals are diagnosed on the basis of clinical symptoms alone and some are diagnosed following genetic analysis. Even in the case of genetic analysis there are a number of possible mutations and the accuracy of diagnosis may depend upon the test(s) that are performed. In any case, it is clear from studies which suggest the likely incidence and prevalence rates of RTT that there are large numbers of undiagnosed individuals in every country, even when services are relatively well-coordinated and the syndrome is well-known amongst the professional community. In the near future, however, the application of new molecular techniques such as whole exome- and whole genome sequencing, especially if applied to new-born bloodspot screening, may lead to the detection of MECP2 mutations even before the characteristic clinical features of Rett syndrome appear (http://www.genomes2people.org/babyseqproject/). Of course, the blanket application of such screening should only be considered if the early findings of the pilots are clinically actionable.

The reversal of the symptoms of RTT in mice has excited interest amongst families such that the ultimate goal in the minds of most families, and hence, most associations, is to find the 'cure'. Some of the larger parent associations are in a position to contribute funding towards basic research in this area as well as being in a stronger position to lobby politically within their own countries for recognition of the syndrome. Families and associations are realistic, however, and recognise that a cure will not be forthcoming immediately. Thus they aim for a better quality of life for their children (of whatever age) in the here and now. This translates into parent associations acting as support networks for families, sharing knowledge and information, offering training where they are in a position to do so and pushing for the creation of centres of expertise and networks of knowledgeable and specialised professionals wherever possible. Few of the parent associations receive state funding and rely on fund-raising, donations and grants. The level to which this can be achieved naturally varies between countries, leading to disparities in services and support between countries. National parent associations gain strength in banding together to form a strong European network (as seen, for example, in RSE), both for lobbying purposes at a European level and as a practical way for countries to offer support to each other. The declaration signed by RSE and the conference organising committee on the final day of ERSCM2013 gave a clear signal that parents across Europe are united in their determination to see the ambitions of the European Commission policy on rare diseases, as well as their own specific wishes in relation to the treatment and cure of RTT, realised.

A co-ordinated European Reference Network for 'Rare neurological diseases', which includes RTT within its remit, will strengthen existing services for RTT, facilitate diagnosis, advice and support for individuals and families in countries which are currently under-resourced, and will allow for the referral of individuals between countries in order to seek diagnosis and treatment. In addition, the model established by the first four European Rett Syndrome Con-

Expert Group on Rare Diseases. The final meeting of the EUCERD Joint Action was on 15th September 2015.

[12]See http://ec.europa.eu/health/rare_diseases/docs/20150610_erns_eucerdaddendum_en.pdf

ferences, bringing together professionals and families to share updates on the most recent developments in research, treatment and management of RTT, has set an invaluable precedent which should be continued. Such pan-European collaborations can only be to the benefit of individuals with RTT and their families.

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ORIGINAL ARTICLE

Burden and drivers of health-related quality of life among French and Italian caregivers of Huntington's disease patients

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Abstract

Objective. To assess the impact of Huntington's disease (HD) on caregivers and identify the main determinants of French and Italian caregivers' burden, and Health-Related Quality of Life (HRQoL).

Methods. This cross-sectional, observational study included patients and their caregivers who were identified by national HD patients associations in France and Italy. Data on HD characteristics and QoL of patients and caregivers was collected using the Huntington Self-Assessment Instrument (HSAI), SF-36 and EQ-5D.

Results. The study included 175 patient caregiver pairs from France and 126 pairs from Italy. Mean age (±SD) of patients was 54.5 (±11.6). Average ages at the onset of the first symptoms and at HD diagnoses were 44.8 (±12.4) years and 46.7 (±12.0) years, respectively. The mean age (±SD) of caregivers in France and Italy was 61.31 (11.36) and 51.14 (13.18) respectively. 44% and 55% of caregivers were unsatisfied with their own happiness and 38% and 45% were unsatisfied with overall QoL in France and Italy respectively. No correlation was found between patients and caregivers HRQoL. Correlations of HDQoL-C scores with patients EQ-5D utility score ranged from 0.16 to 0. 25 and with patients SF-36 ranged from 0.11 to 0.34. Caregivers HRQoL was driven by patient voluntary movement disorder (p=0.01), patient depression/anxiety issues (p<0.01) and patient psychotic disorder (p<0.01).

Conclusion. This study captured the predictors of burden in HD caregivers and provides further insights into HD caregivers. Predictors were found to be voluntary movement disorders, depression/anxiety, and psychotic disorders, thus highlighting further insights for a correct therapeutic approach.

Key words

Caregiver, Health-Related Quality of Life, Huntington's disease.

Background

Huntington's disease (HD) is a rare and chronic neurodegenerative disease causing motor and non-motor disorders that result in progressive disability [1,2]. The disease has a large impact on patients' physical well-being but also on psychosocial functioning, including emotional health, social function, and cognitive dysfunction [3]. As a result, HD affects the Health-Related Quality of Life (HRQoL) of patients but also of their caregivers [4]. As with other caregivers of adults with impairments in cognition and emotional functioning, HD caregivers reported multiple aspects of emotional distress [5]. Caregivers of HD patients described being a carer as 'experiencing the disintegration of one's life' [6]. Besides worrying about everyday coping, carers are also concerned about the risk of their children inheriting the disease. There is a paucity of studies conducted to capture the HRQoL of caregivers of HD patients [4,6-8]. In addition, none of these studies used a validated instrument to quantify the experiences of caregivers of HD patients. In order to expand our knowledge of caregiver burden in different cultures, Italian and French caregivers of HD patients were assessed using a battery of validated instruments. The objective of this study was to assess the impact of HD on caregivers and identify the main determinants of French and Italian caregivers' burden, and HRQoL. It was hypothesized that the degree of burden in caregivers would be correlated with severity of patients' disorders, in particular physical dysfunctions.

Method

Study

The European HD burden study (Euro-HDB) was an international, cross-sectional observational study in six European countries (France, Germany, Italy, Spain, Sweden and UK) and was later extended to Poland and USA. The survey was designed as self-reported interviews. A non-random convenience sampling was used. Patients and their caregivers were contacted by the national HD patient associations: the *Association Huntington France* in France and the *Lega Italiana Ricerca Huntington e malattie correlate onlus (www.lirh.it)* with the support of a neurologist in Italy. The associations were responsible for sending self-reported questionnaires to their members, as well as an information letter explaining the study objectives. The response rate was roughly 70% considering patients who were reached through patient associations. Patients aged at least 18 years old with a well-established diagnosis of HD were asked to participate in the survey and to ask their main caregiver to participate as well. If agreed, patients and caregivers had to fill in two extensive questionnaires, one addressed to the patient and one addressed to the caregiver, and send them back anonymously to the associations. Patients and caregivers were explained that participating to this survey was not compulsory and they gave their consent implicitly by sending back their questionnaires. This study was designed to have no interference on either patient care or caregivers and patients' day to day lives. The recruitment for the study in France and Italy took place from October 2009 to February 2010.

2.2. Assessments

Patients and caregivers completed the Huntington Self-Assessment Instrument (HSAI). In addition, patients were asked to complete the SF-36 and the EuroQoL-5D instruments.

The HSAI is a comprehensive instrument that assesses all HD characteristics. It consists of two questionnaires, one for the patient and one for the caregiver. Both are made up of four parts: background information assessment, the Huntington clinical self-reported instrument (H-CSRI), a disease-specific HRQoL assessment and the Huntington resource utilization interview (H-RUI). This instrument was co-developed and validated in Italian and French.

The H-CSRI is the first clinimetric patient-assessed scale for patients with HD. It includes three subscales:

1. motor subscale including thirteen Likert-type items in four dimensions: voluntary movement, stiffness, chorea, precise movement;
2. the functional subscale including seven Yes/No questions;
3. the behavioural subscale including thirteen Likert-type items in four dimensions: depression/anxiety, temper, psychotic disorder, and cognition.

Higher scores on the function scales indicate more severe symptoms than lower scores. This instrument showed satisfactory validation as demonstrated using classical test and item response assessments [9].

Patients' severity was also measured by the independence scale, a scale included in the Unified Huntington's Disease Rating Scale [10]. It is presented as a checklist of common daily tasks graduated from *'patient doesn't need special care'* to *'patient has a tube fed and has a total bed care'*. It is rated from 0 to 100. Higher scores on the function scales indicate better functioning than lower scores. In this study, caregivers were asked to complete it.

The disease-specific HRQoL assessment of patients was made by the Huntington Quality of Life Instrument (H-QoL-I). It is the first self-reported specific instrument developed to assess the HRQoL of patients with HD. It includes eleven five-point Likert scale items, split into three dimensions: motor functioning (four items), psychology (four items) and socializing (three items). Higher scores on the function scales indicate better HRQoL than lower scores. It demonstrated very good psychometric properties: acceptable construct and external validity and good reliability [11].

The disease-specific HRQoL assessment of caregivers was made by the Huntington's disease Quality of Life Battery for Carers (HDQoL-C) short- version. The HDQoL-C is a multidimensional, disease-specific and subjective HRQoL tool that incorporates the individual's physical health, psychological state, level of independence, social relationships and personal beliefs [12]. The shortened version comprised two components relative to QoL: the satisfaction with life component including three items (section 1) and the feelings about living with HD including seventeen items (section 2). Response choices were presented as a rating scale from dissatisfied or never (scored 0) to satisfied or always (scored 10), respectively, for the first and second component. A total score summarizing the two components is also calculated. For aggregated scores, higher scores on the function scales indicate better HRQoL than lower scores. This instrument showed good internal consistency, reliability and congruent validity [13].

The SF-36 instrument is a standardized generic questionnaire comprising 36 questions designed to assess self-perceived health status. It is a psychometric measure that produces a profile of eight dimensions: physical functioning, role-physical limitations, bodily pain, general health, vitality, mental health, role-emotional limitations, social functioning. Standard scoring algorithms allow aggregation of scores from the eight subscales in two distinct, higher-order summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS) [14]. Higher scores on the function scales indicate better HRQoL than lower scores. The instrument is available in Italian and French. Validation of this instrument is very well documented [15-17].

The EuroQoL-5D self-assessment questionnaire mea-

sures five dimensions of quality of life: mobility, personal care, routine occupations, pain and discomfort, anxiety and depression. Each of these domains is noted on three level Likert-type items: no problem, minor problems, and major problems. The instrument is available in Italian and French. Validation of this instrument is very well documented [18,19].

Data analysis

The EuroQol-5D scores were converted to utility scores from -0.594 to 1 using the UK social tariff [20].

Impact of HD on caregivers is described through the means and Standard Deviation (SD) of HDQoL-C items and aggregated scores.

Pearson's correlations between the two sections and total HDQoL-C scores and 1/the SF-36 scores (the eight dimensions scores and the two summary component scores), 2/the H-QoL-I scores (the three subscales and the total scores) and 3/EuroQol-5D utility score were calculated to investigate the relationship between caregivers' HRQoL and patients' HRQoL.

In order to identify the determinants of caregiver HRQoL, regression analyses were run using the HDQoL-C total score as a dependent variable. Potential drivers were patients' clinical impairments related to the following aspects: motor disorders, depression and anxiety, psychotic disorders, cognition, and temper. Motor disorders, which were composed of voluntary movement disorders, fall and balance disorders, and chorea, were analysed all together as an aggregated variable but also separately as three distinct variables. Analyses were adjusted for age, sex and occupational categories. Several forms of models were tested: traditional linear model, Poisson model, log model and negative binomial model. The model with the lower Root Mean Squared Error (RMSE) was retained.

Results

One hundred and seventy five patient-caregiver pairs in France and 126 pairs in Italy were included in this study. Patient characteristics did not differ between patients from France and Italy. Patient mean age (±SD) was 54.5 (±11.6) years old. Average ages at the onset of the first symptoms and at HD diagnoses were 44.8 (±12.4) years and 46.7 (±12.0) years, respectively. In 90% of the cases, patients reported a performed genetic confirmatory test. All levels of patients' severity were represented (Figure 1). Demographic characteristics of caregivers are shown in Table 1. French caregivers were older than Italian caregivers (61 versus 51 years old, in average) and most of the caregivers did not work (55% for France, 56% for Italy).The vast majority of caregivers were close relatives of the patients, and most of them cared for HD patients on a permanent basis, with a mean duration of caregiving of 16.3 (±19.3) and 9.1 (±7.9) years, respectively for France and Italy.

Caregivers reported taking care of patients' toilet visits, eating, dressing, grooming, walking and bathing for an average time of three hours and a half a day (2.7; 5.0 hours a day respectively for France and Italy). Likewise, they reported four hours per day to take care of shopping,

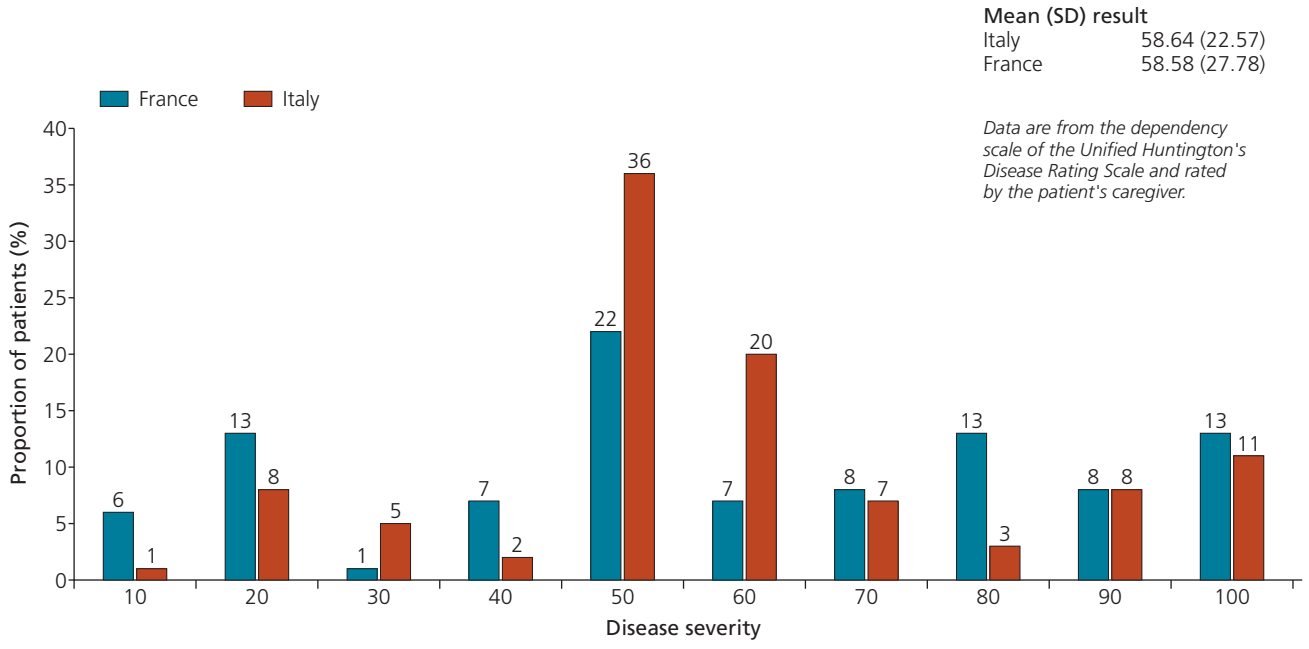

Figure 1. Distribution of patients' severity.

Table 1. Caregivers' characteristics

Characteristics	France n. = 175	Italy n. = 126
Demographic		
Men, n (%)	69 (39%)	50 (40%)
Age (years)	61.31 (11.36)	51.14 (13.18)
Occupational activity		
Workers, n (%)	77 (45%)	55 (32%)
Retired, n (%)	83 (48%)	33 (19%)
Unemployed, n (%)	12 (7%)	38 (22%)
Marital status		
Married/cohabiting, n (%)	139 (80%)	102 (81%)
Never married, n (%)	3 (2%)	13 (10%)
Divorced/separated, n (%)	8 (5%)	4 (3%)
Widowed, n (%)	23 (13%)	7 (6%)
Family situation		
Main carer, n (%)	133 (78%)	110 (90%)
Carer lives with HD patient, n (%)	118 (68%)	101 (80%)
Number of years since HD knowledge in family	22.3 (20)	13 (9.8)
Have children at risk, n (%)	92 (56%)	68 (55%)
Relation with HD patient		
Husband/wife, n (%)	118 (70%)	75 (60%)
Child, n (%)	19 (11%)	12 (10%)
Sibling, n (%)	11 (7%)	10 (8%)
Parent, n (%)	16 (9%)	18 (15%)
Friend, n (%)	1 (1%)	2 (2%)
Other, n (%)	3 (2%)	7 (6%)
Carer background		
Carer has previously cared any other HD-affected person, n (%)	44 (25%)	27 (21%)
Duration of caring (in years)	**16.3 (19.3)**	**9.1 (7.9)**

food preparation and housekeeping (2.7; 5.1 hours a day, respectively); almost five hours per day to assist patients in their care (1.2; 6.8 hours a day, respectively) and five hours and a half per day to supervise patients (2.9; 6.0 hours a day, respectively).

With regards to their own happiness, 44% and 45% of caregivers declared themselves to be unsatisfied respectively in France and in Italy. Similarly, 38% and 45% declared themselves to be unsatisfied with their overall quality of life. They reported [mean (±SD)] to be stressed [5.51 (±2.91); 6.38 (±3.39)], exhausted [5.53 (±3); 5.49 (±2.89)], and felt that their needs were not important to others [6.49 (±2.64); 5.15 (±3.64] respectively for France and Italy. Most importantly, they were very worried about the genetic consequences of HD [7.89 (±2.86); 8.18 (±3.38)]. However, they reported as well to have hope for the future [5.63 (±3.28); 5.63 (±2.85)] and especially they believe that a cure for HD will be found one day [5.75 (±3.06); 7.06 (±2.57)]. They felt they could cope [5.7 (±2.78); 6.95 (±3.4)] and even felt that HD made them a stronger person [5.35 (±3.11); 6.45 (±2.92)]. The French HDQoL-C scores were 53.21 (±25.14) and 48.75 (±14.78) respectively for satisfaction regarding different areas of life and feelings with regards to different aspects of life dimensions. The equivalent Italian HDQoL-C scores were 49.33 (±28.93) and 53.94 (±16.43). There was no difference in the global HDQoL-C scores between the two countries (p=0.77).

HRQoL of caregivers was not found to be related to HRQoL of patients as illustrated by Figure 1, displaying the HDQoL-C total score in function of the EuroQoL-5D utility score, but also by the Pearson's correlations between patient and caregiver HRQoL scores. Indeed, HDQoL-C scores were found to be weak to moderately correlated with the generic patient HRQoL assessments. Correlations between HDQoL-C scores and the EuroQoL-5D utility score ranged from 0.16 to 0.25. Correlations between HDQoL-C scores and the eight domains of SF-36 instruments varied from 0.11 to 0.34 (Table 2). Similarly, HDQoL-C scores were found to be weakly to moderately correlated by the specific patient HRQoL instrument (H-QoL-I) with a range of 0.24 to 0.34.

Analysis of determinants retained the traditional linear model which modelled the dependent variable, i.e. HDQoL-C total score, as normally distributed using an identity link function. The RMSE was 15.56 (range: 15.56-16.55), 16.02 (range: 16.02-16.89) respectively for France and Italy. Drivers of caregiver's HRQoL, explained by the total HDQoL-C score, were found to be patient voluntary movement disorder (p=0.01, p=0.03 respectively for France and Italy), patient depression/anxiety issues (p<0.01), patient psychotic disorder (p<0.01). Figure 2 illustrates the relationship between the caregiver's HRQoL and patient voluntary movement disorder. Patient cognition, temper and chorea were not found to be determinants of caregivers' HRQoL independent of other clinical characteristics (Table 3).

Discussion

HD is characterized by progressively worsening motor, cognitive, behavioural and psychiatric symptoms. Emergence and sequence of symptoms vary from one patient to another but HD is fatal for all. As the disease progresses, motor disturbance becomes more and more generalised and patients' concentration on cognitive tasks becomes increasingly difficult until the complete physical dependence. In parallel, the burden for family increases in a substantial way [2]. The literature is scarce on issues of caregivers' of HD patients with no previous studies conducted on the topic in France and Italy.

Table 2. Pearson's correlations between caregivers' HRQoL, as measured with the HDQoL-C instrument and patients HRQoL, as measured with the EQ-5D, SF-36 and H-QoL-I instruments

	EQ5D	SF36										H-QoL-I			
HDQoL-C	Utility	PF	RP	BP	GH	VT	MF	RE	SF	PCS	MCS	PF	Psych.	Social.	Total
Section 1	0.25	0.22	0.24	0.11$^{\mu}$	0.31	0.34	0.26	0.28	0.32	0.25	0.27	0.31	0.26	0.29	0.33
Section 2	0.16	0.15*	0.18	0.1$^{\mu}$	0.28	0.26	0.21	0.20	0.20	0.21	0.25	0.24	0.24	0.30	0.30
Total	0.24	0.21	0.24	0.12$^{\mu}$	0.33	0.34	0.27	0.26	0.29	0.25	0.28	0.31	0.27	0.31	0.34

All correlations were significant at 1% level except where indicated by * or $^{\mu}$.
*: significant at 5%; $^{\mu}$: non-significant.
Section 1: satisfaction regarding different areas of life. Section 2: feeling regarding different aspects of life.
BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary ; PF; physical functioning; Psych., psychology; RE, role limitations due to emotional problems; RP, physical problems; SF, social functioning; Social. , socializing; VT, vitality.

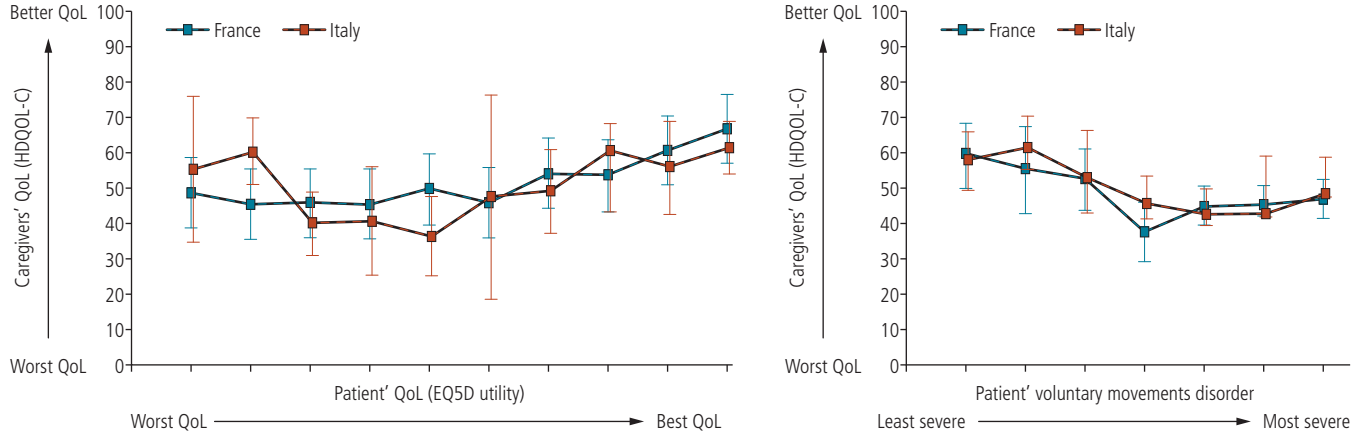

Figure 2. HDQoL-C total score according to patients' QoL (left panel); HDQoL-C total score according to patients' voluntary movement disorder (right panel).

Table 3. Results of regression model on HDQoL-C

		France			Italy		
Variables	Degree of freedom*	Chi-square test	β coefficient	p-value	Chi-square test	β coefficient	p-value
Voluntary movements	1	6.33	-1.96	0.01	5.80	-1.47	0.03
Fall/balance	1	0.32	0.25	0.57	2.40	0.52	0.051
Chorea	1	1.6	0.63	0.21	1.26	0.79	0.26
Depression/anxiety	1	11.37	-1.45	<0.01	8.28	-1.59	<0.01
Temper	1	3.44	1.81	0.06	1.43	1.67	0.23
Psychotic disorder	1	8.29	-1.73	<0.01	6.66	-1.23	<0.01
Cognition	1	1.8	-0.68	0.18	1.32	-0.46	0.25
Sex (Female)	1	2.24	-5.51	0.13	2.69	-7.89	0.10
Occupational activity	7	19.39	positives	<0.01	13.67	positives	0.05
Age	1	0.81	0.18	0.37	1.01	0.22	0.31

*Results from the regression model with the dependent variable, HDQoL-C total score, normally distributed and with the use of an identity link function (RMSE 15.56; 16.02 respectively).

This study found that HD patients are assisted by their family, in particular by their husband or wife (70%) but also by their children (10%). Caregivers spent a substantial amount of time caring for HD patients, as they reported caring their relative for almost 10 hours a day in France and almost the entire day (i.e. 23 hours) in Italy; those times did not include time dedicated for transportation. As a result, Italian relatives reported spending more than twice the time caring for patients on average than French relatives. Across both Italian and French results, global caregiver HRQoL was highly affected and in particular caregivers felt stressed and exhausted; they believed that their needs were not important to others and above all they were very worried about the genetic consequences of HD.

Caregiver HRQoL was found to be indirectly correlated through patient clinical scores. As such, caregivers' HRQoL worsens as the patient's clinical characteristics deteriorate, especially in terms of voluntary movement disorders, depression/anxiety and psychotic disorders. A previous study investigated the determinants of HD patients and caregiver self-report QoL and established that patient and caregiver QoL was associated with functional capacity and cognitive scores [4]. Unfortunately, it was complicate to directly compare the results from the two studies, as previous researchers investigated QoL and not HRQoL and as such the assessments were very different. In this present study, the association between functional capacity and HRQoL was not directly analysed. However, it was found that voluntary movement disorders were associated with lower HRQoL, which could be considered a good determinant of functional capacity. Finally, although Ready et al (2008) previously found that neuropsychiatric symptoms were not associated with caregivers' QoL, the authors explained that this unexpected result was possibly a type II error due a low study power.

This study had a number of strengths and weaknesses. Strong points included the use of validated HD-specific instruments and the inclusion of patients and caregivers with wide range of age, years of evolution and stages of the disease. Another point of strength was the large number of patients and caregivers who participated in this study, given that HD is an orphan disease. This was possible due to the design of the study and the collaboration with patients associations. However, this design potentially led to a biased selection due to recruitment from only patient associations and thus institutionalized patients were possibly under-represented. Also, it is important mentioning that results could have been different if clinical severity had been assessed by clinicians instead of patients themselves. Several studies reported divergence in patient and professional views of clinical outcomes [21,22]. However, because patient reported outcome questionnaire was developed based on the clinician questionnaire, it is likely that patient assessment and clinician assessment are very correlated even not the same and results would not have been dramatically different. But this should be carefully investigated in future studies.

Conclusion

In conclusion, this study provides further insights into HD caregivers and captures the predictors of burden in HD caregivers. Predictors were found to be voluntary movement disorders, depression and anxiety, and psychotic disorders. Further research needs to be conducted to more fully understand those determinants and confirm these findings.

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Case Report

Fahr's disease with epilepsy, deafness, schizophreniform psychosis and autoimmune polymyositis: a case report

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Abstract

Fahr's disease is a rare sporadic or inherited neurodegenerative disorder characterized by symmetrical bilateral calcifications in the basal ganglia and some other brain structures – dentate nucleus, thalamus, cerebral cortex, subcortical white matter, and hippocampus.

We report a patient with Fahr's disease who was monitored for 11 years. The case is of interest for clinical practice because of the following features: 1. the patient fulfills the Fahr's disease criteria with the exception of family history consistent with autosomal dominant inheritance; 2. early disease onset (20 years of age) with a generalized tonic-clonic seizure; 3. despite calcifications in the region of the basal ganglia on CT scans, there are no clinical signs of extrapyramidal system abnormalities; 4. rare epileptic seizures (4 generalized tonic-clonic seizures for the whole period of observation); 5. generalized paroxysmal activity of delta waves on only one EEG which could not be regarded as a specific finding; 6. autoimmune polymyositis as a concomitant disease, which improved by specific treatment; 7. diagnosis of complete deafness 6 years after Fahr's disease onset; 8. typical psychotic symptoms 9 years after the first epileptic seizure; 9. Fahr's disease evolution was proven 11 years after initial symptoms by CT scan visualization of new bilateral symmetrical calcifications in the cerebellar hemispheres and respective clinical manifestations – static and locomotor ataxia. We found no case reports in the literature with a similar combination of clinical manifestations and progression.

In conclusion, this case report provides additional information about the clinical characteristics and management of patients with Fahr's disease.

Key words

Fahr's disease, epilepsy, psychosis, polymyositis, deafness.

Introduction

Fahr's disease (familial idiopathic calcification of the basal ganglia) was first described by the German neurologist Theodor Fahr in 1930 [1]. It is a rare (prevalence of <1/1,000,000) sporadic or inherited neurodegenerative disease characterized by symmetrical bilateral calcifications in the basal ganglia and some other brain structures – dentate nucleus, thalamus, cerebral cortex, subcortical white matter, and hippocampus [1, 2]. It has been recognized as a sporadic or inherited disease with identified loci in chromosomes 2, 8 and 14q and autosomal dominant type of inheritance [2-4].

The most frequent initial symptoms are associated with extrapyramidal system disorders [1], including Parkinson syndrome [2], choreoathetosis [5] and dystonia [6]. Other symptoms include coordination impairment [1, 2], dysarthria [1, 2], psychiatric disorders (depression, anxiety, visual, auditory hallucinations, delusions, mania, personality and behavior problems, schizophreniform psychoses, delirium) [1-3, 7-9], cognitive impairment as a part of subcortical dementia (impaired verbal, visual-spatial memory, planning, attention, concentration, visual constructive abilities) [10-11]. Epileptic seizures (complex partial seizures) [2, 12], stroke-like incidents [2], vertigo [2], headache [2], paresis [2], orthostatic hypotonia [1, 2] have been rarely described.

Diagnostic methods: 1. CT scan – a basic method, more effective than MRI; 2. SPECT – it shows increased blood flow in both temporal lobes; 3. EEG – there is no specific EEG pattern [13].

The modern modified criteria of Manyam 2005 for Fahr's disease can be summarized as follows [1]:

1. bilateral calcification of the basal ganglia on neuroimaging. Other brain regions may also be involved;
2. progressive neurologic dysfunction, usually including a movement disorder and/or neuropsychiatric manifestations. Age of onset is typically in the fourth or fifth decade, although this dysfunction may also present in childhood;
3. absence of biochemical abnormalities and somatic features suggestive of a mitochondrial or metabolic disease or other systemic disorder;
4. absence of an infectious, toxic or traumatic cause;
5. family history consistent with autosomal dominant inheritance.

The differential diagnosis includes a variety of inflammatory, toxic, anoxic, metabolic conditions associated with basal ganglia calcifications.

There is no specific treatment [2]. The symptomatic treatment includes antipsychotic drugs [3, 6], antiepileptic drugs [1], antidepressants [1], anxiolytic agents [1].

Generally, the disorder worsens over time and progressive neurological deterioration results in disability and death.

Case report

A 21-year-old male patient was first admitted to the Neurology Clinic at the University Hospital St. George in Plovdiv, Bulgaria, in 2004 with the purpose of diagnosis and adequate treatment.

The patient was born with asphyxia, with subsequent normal neuropsychological development, without clinically significant diseases in childhood. In July 2003, he had a first unprovoked generalized-tonic-clonic seizure, and carbamazepine therapy (daily dose of 300 mg) was initiated. Swelling of the ankles started in October 2003. In April 2004, the patient was admitted to Multiprofile Hospital for active treatment (Plovdiv). He was diagnosed with reactive hepatitis caused by carbamazepine treatment. Carbamazepine was replaced with oxcarbazepine. Then thyroid ultrasound was performed, that was normal. TSH was within reference values.

In November 2004, ankles swelling reappeared. It was accompanied by lower extremities weakness and pain in the leg muscles. The patient became less self-sufficient and that was the reason for which he was admitted to the Neurology Clinic. There was no family history for any disease.

Physical examination

Asthenic habitus, swelling of lower legs, ankles and feet. Subfebrile temperature (37.5 °C) during the first days of hospitalization. Examination of other systems showed no abnormalities.

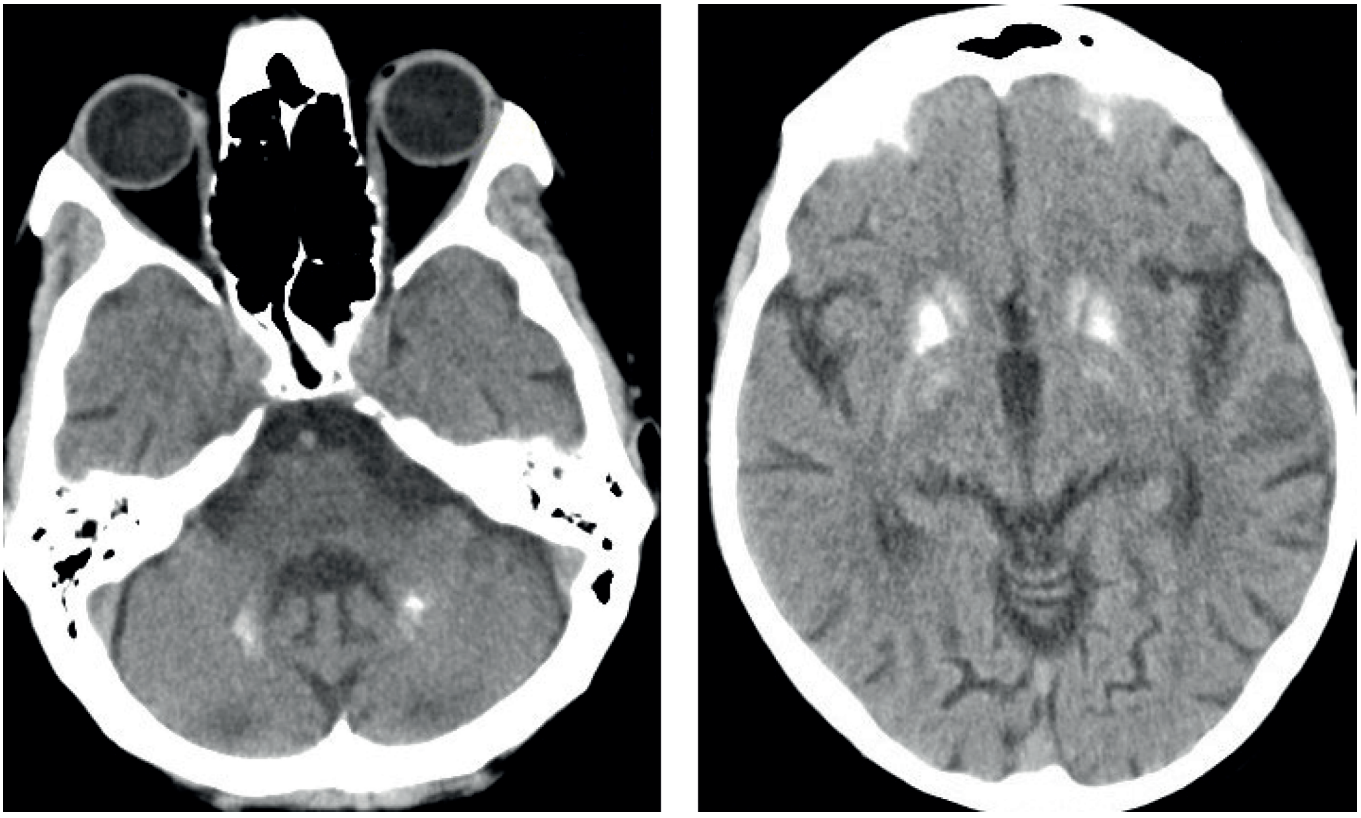
Neurological examination

Conscious, without psychotic manifestations. Amyotrophic syndrome, more severe for the proximal muscles of extremities: reduced power of the legs – reduced power of thigh muscles, limited plantar flexion and impossible dorsal flexion of feet; normal Achilles reflexes; areflexia for triceps and styloradial reflexes, hyporeflexia for biceps reflexes. Spontaneous and palpatory pain of hip and leg muscles. Distal hypesthesia for pain, temperature, and touch of the lower extremities.

Laboratory investigations

1. Within reference values: full blood count, differential blood count, erythrocyte sedimentation rate, blood glucose, cholesterol, total protein, albumin, urea, creatinine, total and direct bilirubin, electrolytes/sodium, potassium, calcium, coagulogram, troponin, serum IgA, IgM, IgG, reversed Ehrlich reaction, cerebrospinal fluid test, serum and urine uroporphyrins and coproporphyrins, Lyme borreliosis test /-/, HIV /-/, Wassermann /-/, HBV antigen /-/ and anti-HCV /-/, LE cells /-/, antinuclear antibodies /-/; parathyroid hormone (30 pg/ml).
2. Abnormal results: AST 105 U/l, 79 U/l; ALT 67 U/l, 37 U/l; alkaline phosphatase 250 U/l, 211 U/l; LDH 1298 U/l, 872 U/l; HBDH 557 U/l, 442 U/l, creatine kinase 1242 U/l, 653 U/l; MB fraction of creatine kinase 124 U/l , GGT 39 U/l, 32 U/l; cholinesterase 3516 U/l, anti Jo-1 /ELISA/ 1:32 /+/. Flow cytometry of the lymphocyte population: mild decrease in T-lymphocytes. Decreased T-killer cells. T-suppressor cell percentage near the upper reference value. Decreased percentage of T-helper cells decreased ratio CD4/CD8: a sign of immune dysbalance.

- X-ray of the lungs showed no active pulmonary disease.
- ECG showed no clinically significant abnormalities.
- CT scan: bilateral symmetrical calcifications in the region of caudate nucleus, putamen, and thalamus.
- EEG showed no abnormalities.
- EMG: on needle EMG test of all investigated muscles /mm. biceps brachii, mm. deltoidei, mm. quadriceps femoris/ we recorded spontaneous denervation activity at rest /fibrillations, fasciculations, multiple positive acute waves/ and action potentials with myopathic (myositis) characteristic during muscle contraction. The disease history, clinical progress, and the recorded denervation activity and reduced conduction of peripheral motor neurons of both proximal and distal segment of legs are consistent with secondary distal, mainly axonal peripheral disorder which we accepted as secondary to chronic polymyositis.
- Abdominal ultrasound: steatosis of the liver. The treatment with carbamazepine was accepted as the most possible explanation for this finding.
- Fibrogastroscopy: chronic gastroduodenitis with erythema and exudates.
- Echocardiography: suspected secondary myocarditis.



Symmetrical small calcifications in both cerebellar hemispheres.

Treatment

Pentoxyfilline 800 mg daily, milgamma N (benfotiamine/pyridoxine hydrochloride/cyanocobalamine) 3 tablets daily, pyridostigmine bromide 2×60 mg daily, oxcarbazepine 300 mg daily, amantadine sulfate i.v. 200 mg/500 ml.

Clinical progress

The patient improved and at the end of hospitalization he was able to stand without help.

Differential diagnosis

1. Hereditary dystrophic myopathy. Rejected because of the rapid progress of amyotrophic syndrome, persisting muscle pains, fever, denervation activity on EMG.
2. Spinal muscular atrophy of Kugelberg Welander. Rejected for the lack of fasciculations from the neurological examination, preserved Achilles, distal hypesthesia of the lower extremities. The spontaneous activity on EMG is not consistent with the abnormal high and continuous action potentials during muscle contraction typical of spinal motor neuron disease.
3. Somatic disease (hepatic, hematological, of the thyroid and parathyroid gland, acute intermittent porphyria).

The diagnosis of autoimmune polymyositis complicated with secondary distal axonal polyneuropathy was based on the following criteria: fever, muscle pains, muscle atrophy, articular edema, increased enzymes, /+/ anti Jo-1, echocardiographic data about secondary myocarditis, EMG results, consultation with rheumatologist. The possibility of polymyositis secondary to carbamazepine and oxcarbazepine treatment was ruled out.

The patient was admitted to the Rheumatology Clinic and was treated with cortisone. The patient was discharged from hospital with significant improvement. Valproate was started for seizures treatment. Azathioprine and prednisone were recommended and initiated for supporting treatment of polymyositis.

Long-term follow-up of the patient

The patient had a second generalized tonic-clonic seizure in 2006. Valproate 1000 mg daily and oxcarbazepine 1200 mg daily were recommended and started. Later oxcarbazeline was discontinued.

The patient had a third generalized tonic-clonic seizure in 2009.

The patient has been with profound deafness since 2009, with externally worn hearing aid.

EEG 39/10.03.2010: a background activity of not well organized alpha rhythm, with weak reaction to eyes opening and photostimulation. Frequent generalized paroxysms of delta waves with duration up to 1 second and maximal amplitude in the frontal regions.

In 2012 the patient was admitted to a Psychiatry Clin-

ic because of anxiety, statements that he "hears noises and that everyone speaks about him and his parents on TV". He spoke more than usual and sought information about his relatives in the newspapers. He was aggressive. During hospitalization hyperbulia, accelerated thought with frequent topic change, paranoid ideation, and non-verbal auditory hallucinations were described. He was diagnosed with paranoid schizophrenia and treatment with haloperidol and biperiden hydrochloride was recommended and started.

The patient had a fourth generalized tonic-clonic seizure in 2014 (treated with valproate 1500 mg daily).

During a second hospitalization in the Neurology Clinic in 2014, impaired coordination with static and locomotor ataxia was found.

EEG 41/26.06.2014: decreased and not well organized brain activity without focal and paroxysmal activity.

CT scan in 2014 visualized massive, symmetrical, bilateral calcifications in the region of basal ganglia (caudate nucleus, lentiform nucleus) and thalamus (see Figure on page 36).

A daily treatment with valproate 1000 mg daily, betahistine 48 mg, vinpocetine 20 mg, azathioprine 50 mg, prednisone 15 mg, haloperidol 1.5 mg, biperiden hydrochloride 4 mg was recommended and started.

Discussion

The reported case is interesting for clinical practice because of the following features:

1. the patient fulfills the Fahr's disease criteria with the exception of family history consistent with autosomal dominant inheritance;
2. early disease onset (20 years of age) with a generalized tonic-clonic seizure;
3. despite calcifications in the region of the basal ganglia on CT scans, there are no clinical signs of extrapyramidal system abnormalities;
4. rare epileptic seizures: 4 generalized tonic-clonic seizures for the whole period of observation. Epilepsy was discussed as a separate condition, but no evidence for other etiology was found from disease history and investigations;
5. generalized paroxysmal activity of delta waves on only one EEG which could not be regarded as a specific finding;
6. autoimmune polymyositis as a concomitant disease, which improved by specific treatment;
7. diagnosis of complete deafness 6 years after Fahr's disease onset. The possibility of being a separate condition was discussed, but no explanation was found;
8. typical psychotic symptoms 9 years after the first epileptic seizure;
9. Fahr's disease progression was documented 11 years after initial symptoms by CT scan visualization of new bilateral symmetric calcifications in the cerebellar hemispheres and respective clinical manifestations (static and locomotor ataxia). We found no case reports in the literature with a similar combination of clinical manifestations and evolution.

Conclusions

In conclusion, this case report provides additional information about clinical characteristics and management of patients with Fahr's disease.

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