Parkinsonism and Related Disorders xxx (xxxx) xxx

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Recognition and characterising non-motor profile in early onset Parkinson's disease (EOPD)

Karolina Poplawska-Domaszewicz [a,b,**], Mubasher A. Qamar [b,c], Cristian Falup Pecurariu [b,d,e], K Ray Chaudhuri [b,c,*]

[a] Department of Neurology, Poznan University of Medical Sciences, 60-355, Poznan, Poland
[b] Parkinson's Foundation Centre of Excellence, King's College Hospital, Denmark Hill, London, SE5 9RS, UK
[c] Basic and Clinical Neuroscience Department, The Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 5 Cutcombe Road, London SE5 9RX, UK
[d] Department of Neurology, County Clinic Hospital, Faculty of Medicine, Transilvania University Brasov, 500019, Brasov, Romania
[e] Department of Neurology, Transilvania University Brasov, Braşov, Romania

ARTICLE INFO

Keywords:
Early onset Parkinson's disease
Parkinson's
Nonmotor
Genetic
EOPD
Late onset Parkinson's

ABSTRACT

Early onset Parkinson's disease (EOPD) has been recently defined as a clinical entity with subjects presenting with Parkinson's disease (PD) between the ages of 21–50 and replaces the term Young Onset PD (YOPD). Presentations in this age group are somewhat different to the typical Late Onset sporadic PD (LOPD) and genetic basis may play an important role. The presentations are however, to be differentiated from other causes of juvenile onset or early onset parkinsonism, which are often driven by rare genetic, brain metal deposition, or metabolic progressive disorders with a levolevodopa unresponsive or poorly responsive phenotype. Specific genetic mutations can also underpin EOPD and include nonmotor symptoms of EOPD, which have not been studied extensively. However, some real-life comparator studies with LOPD suggest a nonmotor profile in EOPD dominated by neuropsychiatric symptoms (anxiety), pain, sexual dysfunction, and a higher risk of impulse control disorders and segregation to the recently described noradrenergic and Park-sleep nonmotor endophenotypes may occur. Awareness of the phenotypic variants and nonmotor expression will pave the way for future precision and personalised medicine.

1. Introduction

Parkinson's disease (PD) is a heterogenous syndromic condition, rather than a single disease [1]. One aspect of the heterogeneity is that PD can present at any age group from the ages of 30 to the 90s, with sharply rising prevalence over the age of 70 [2]. The US National Institute on Aging estimated that 5–10 % of all cases of PD occurs before the age of 50 year and are collectively referred to as Early Onset PD (EOPD), whilst the American PD Association has suggested that EOPD occurs in 10–20 % of PD and as such there may be about 6000–12,000 people in the United States alone [3,4]. The International Movement Disorders and Parkinson's society (MDS) task force on EOPD attempted to define this group and proposed a definition of PD with an age of onset after 21 years but before 50 years [5], with urge to use the term EOPD, rather than YOPD. The issue of EOPD is of major societal and medical concern in many developing countries and as an exemplar in India which carries one-sixth of the world's population and is likely to have the highest absolute number of PD patients in the world, 40–45 % may have age of onset of motor symptoms between 22 and 49 years and as such have EOPD [6] (Table 1).

EOPD needs to be distinguished from early onset parkinsonism (EOPism), which is beyond the scope of this review. EOPism occurs secondary to a range of monogenic genetic disorders, metabolic, metal deposition, infection related causes, as well as with dystonia and ataxia, either in a chronic progressive manner or acutely [7]. EOPism usually presents before 21 years of age and usually present with many non-parkinsonian symptoms which do not rresemble typical features of PD.

Nonmotor symptoms (NMS) of PD are ubiquitous and present at all stages of PD and are important markers for the prodromal period of PD

* Corresponding author. Parkinson's Foundation Centre of Excellence, King's College Hospital, Denmark Hill, London, SE5 9RS, UK.
** Corresponding author. Parkinson's Foundation Centre of Excellence, King's College Hospital, Denmark Hill, London, SE5 9RS, UK
E-mail address: ray.chaudhuri@kcl.ac.uk (K.R. Chaudhuri).

https://doi.org/10.1016/j.parkreldis.2024.107123
Received 15 May 2024; Received in revised form 15 August 2024; Accepted 31 August 2024
Available online 5 October 2024

[8–10]. NMS ranges from cognitive, neuropsychiatry, sleep, autonomic dysfunction, and the overall burden of NMS is a major determinant of quality of life (QoL) in PD [11,12]. In addition, more recently NMS dominant endophenotype of PD, the nonmotor subtypes have also been described [13]. EOPD therefore, also expresses a range of NMS, which could be either those continuing from prodromal stage or develop once diagnosis has been made (Fig. 1). In EOPD, the known genetic mutations of PD may play a more prominent role in pathophysiology compared to late-onset PD (LOPD) and genes have also been linked to some specific NMS. In this review we discuss the range and nature of NMS in EOPD as well touch upon subtypes and personalised management strategies.

This is a narrative review as the topic is specialised and literature specifically dealing with NMS in EOPD is scarce. Search in English language regarding relevant literature using EOPD, NMS, Genetic, Prodromal, NMS subtypes, Early onset parkinsonism, Juvenile onset PD, Middle Onset PD, Late Onset PD were performed using PubMed, Google Scholar as well as searching the existing PD nonmotor group database.

2. Prodromal nonmotor symptom and EOPD ’

A range of NMS occur in the prodromal phase and there is extensive literature related to the likelihood ratios of prodromal symptoms leading to manifested diagnosis of clinical Parkinsonism [14]. Several NMS occur in Prodromal NMS with varying frequencies and range from rapid eye movement behaviour disorder (RBD), hyposmia, constipation, depression, excessive daytime sleepiness, erectile dysfunction, fatigue, focal pain as well as apathy and loss of colour vision. In relation to EOPD there are studies attempting to predict diagnosis of PD. One such study is the prospective evaluation of risk factors for Idiopathic Parkinson’s Syndrome (PRIPSP) study, which although not targeting EOPD included relatively younger participants with a mean age of 59 years and reported that a combination of pre-screening for age, a positive family history, and/or hyposmia, and secondary screening for enlarged substantia nigra hyperechogenic using ultrasound predicted development of PD [15]. Some suggest NMS to signpost a genetic aetiology in EOPD; pathogenic glucocerebrosidase (*GBA1*) mutations (typical age of onset 4th-8th decade) may, for instance, be associated with prodromal rapid eye movement behavioural disorder (RBD) and dysautonomia. Some authors suggest that *GBA1* mutations may have an EOPD and some could develop PD before 50 years of age and also carry a higher risk and earlier presentation of NMS (RBD, dysautonomia, psychiatric manifestations) compared with LOPD [16]. However, some prodromal NMS, such as RBD or hyposmia typically found in patients with late onset PD appear to be rarer in EOPD [7,16,17].

3. Carriers of genetic mutations, nonmotor symptoms and EOPD

Several genes have been associated with EOPD (Table s2,3). In younger people with EOPD, especially people who may have multiple family members with PD, genetics may be a strong factor to consider and for instance some genetic mutations, such as *PRKN* gene, are associated with an increased risk of EOPD [18]. The phenotype may vary from typical PD phenotype to atypical as in those with *PLA2G6* mutations, while commonly established mutations, such as *LRRK2*, may not be relevant in EOPD, as there is low penetrance before the age of 50.

Table 1
A summary of published observational studies addressing motor and nonmotor symptoms in early onset PD.

Type of PD	Comparator	Validated tools	Key NMS outcomes	REF
EOPD (onset 21–45yrs)	Late onset PD	NMSQuest	MMSE significantly higher, HDRS significantly lower. Anxiety rate similar NMSQ total Score: 7.7 ± 5.8 (YOPD) vs 11.9 ± 6 ($p < 0.05$).	[53]
EOPD group (<45 years)	middle-age onset group (45–64 years) old-age onset group (≥65 years)	MMSE, HDRS, HARS, ESS, PDSS	MMSE significantly better in EOPD. PDSS and ESS in normal range compared to abnormal in LOPD	[54]
EOPD (<49yrs)	MOPD (50–69yrs) LOPD (>70yrs	Retrospective chart review	Depression in EOPD (48.3 %) vs. LOPD (22 %). Similar rates of other NMS.	[55]
EOPD (mean 47.4 yrs)	Age matched controls	QUIP short	49 (58.3 %) displayed an ICB, versus. 28 of the 87 HCs (32.9 %; $p = 0.001$).	[56]
EOPD (<50 years)	MOPD (50–69yrs) LOPD (>70yrs)	MOCA, GDS, STAI, RBDSq, ESS, SCOPA-aut	EOPD significantly higher MOCA. Significant more anxiety (STAI trait). Significantly less GIT, Urinary and sexual dysfunction.	[57]
EOPD (<45 years)	HCs	BDI, Scopa AUT, QUIP, BSFI	SCOPA aut scores significantly worse in EOPD vs. HCs. Worse sexual dysfunction. Worse pain and increased hypersexuality.	[58]
EOPD (51.48 years)	MOPD, LOPD	MMSE No other details are provided	Significant higher rates of non-depression psychiatric features (22.2 %), Low rates of dementia and autonomic dysfunction.	[59]
EOPD (onset 49 years)	MOPD (50–69yrs) LOPD (>70yrs)	NMSS	EOPD report significantly less cardiovascular falls, cognitive dysfunction, hallucinations, and pain.	[60]
EOPD (<50 years)	Nil	BDI, MMSE, KPPS, NMSS	Pain in 107/135 (79.3 %). BDI and NMSS significantly higher in those with pain.	[61]
EOPD (mean 51.4 yrs)	Late onset PD	RBDSq, Neuropsychiatric questions (?), ICD	28.5 % RBD, 29 % constipation, similar rates of neuropsychiatric complications to LOPD 37.3 % rates of ICD.	[62]
EOPD (21–45 years) Sporadic and Familial	Controls	ESS, RDBSQ, PSQI, HADS, NMSQ, NMSS, MOCA, QUIP	ESS, HADS, RBDSQ, NMSQ, QUIP scores worse in EOPD vs. controls. NMS burden was very severe in 40 % familial EOPD vs 9.1 % sporadic EOPD.	[63]
EOPD (mean 51 ± 11 yrs)	Cohort survey 2035 patients	Chart review	Family history of tremor or parkinsonism in 6.19 % (n = 126), majority had onset of symptoms in the right side (55.92 %), tremor was the most prevalent symptom at onset. Psychosocial issues in EOPD reported.	[64]
EOPD (21–40yrs)	JOPD	Cognitive function, autonomic function, CSF	15 % of JOPD cases had no rest tremor and dystonia (43 %) and autonomic symptoms (42 %) were more frequent in JOPD compared to EOPD (tremor 9 %, autonomic 17 %).	[65]

AUT autosomal dysfunction; BDI Beck’s Depression Inventory; BSFI Brief Sexual Function Inventory; EOPD early onset Parkinson’s disease; ESS Epworth sleep scale; GDS Geriatric Depression Scale; GIT gastrointestinal tract; HARS Hamilton Anxiety Rating Scale; HC healthy controls; HDRS Hamilton Depression Rating Scale; ICB impulsive compulsive behaviour; ICD impulsive compulsive disorders; KPPS King’s Parkinson’s Pain Scale; LOPD late onset Parkinson’s disease; MMSE mini mental state examination; MOCA Montreal cognitive assessment; MOPD middle onset Parkinson’s disease; NMS nonmotor symptoms; NMSS nonmotor symptoms scale; PD Parkinson’s disease; PDSS Parkinson’s disease sleep scale; QUIP Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s disease; RBDSq Rapid eye movement behaviour disorder screening questionnaire; SCOPA scales for outcomes in Parkinson’s disease; STAI State-Trait Anxiety Inventory; YOPD young onset Parkinson’s disease; JOPD juvenile onset Parkinson’s disease; CSF cerebrospinal fluid.

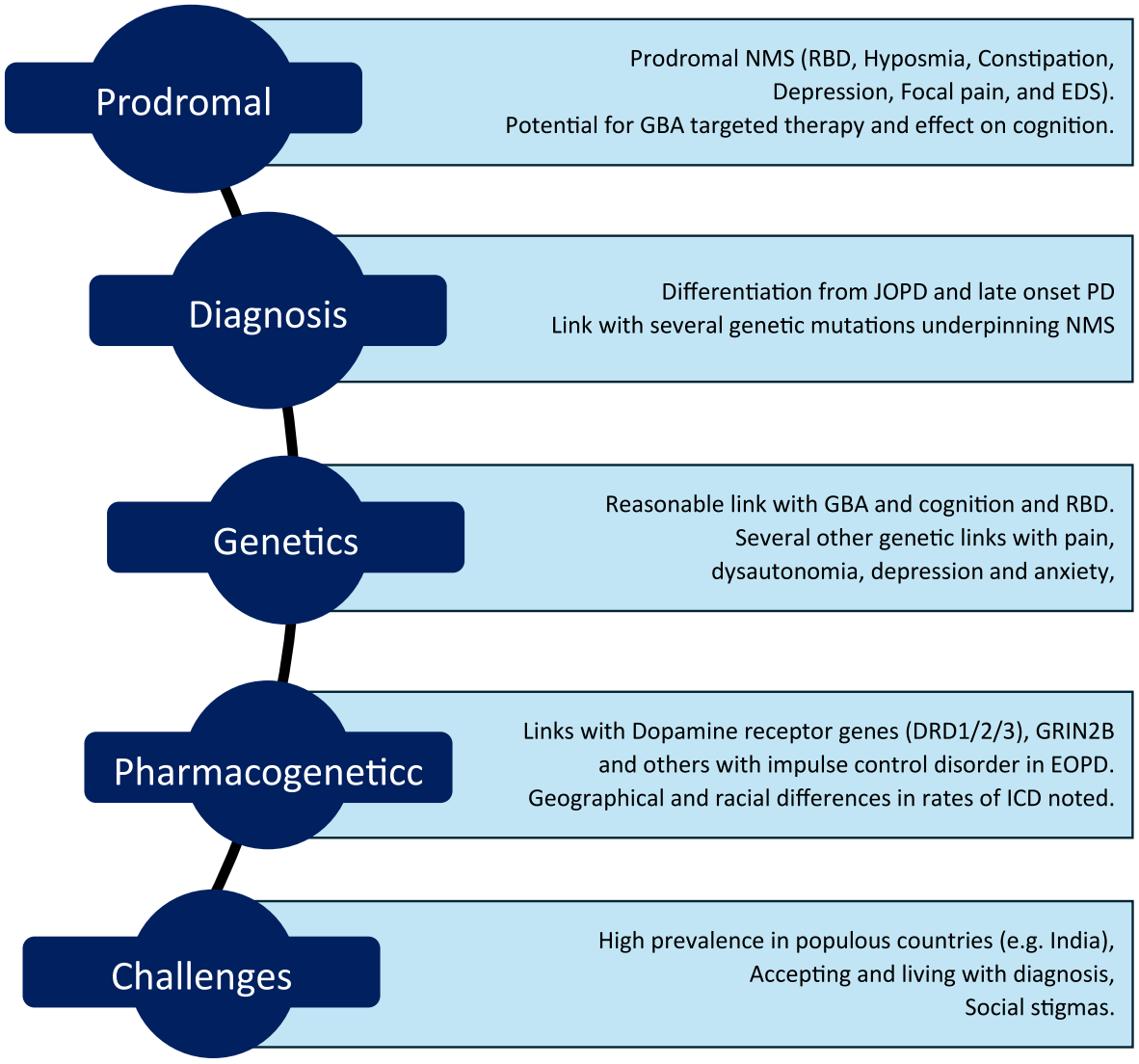

Fig. 1. A schematic conceptual visualisation of the spectrum and evolution of nonmotor symptoms in Early Onset Parkinson's Disease.
EDS *excessive daytime sleepiness*; EOPD *early onset Parkinson's disease*; GBA glucocerebrosidase; ICD *impulsive compulsive disorder; JOPD juvenile onset Parkinson's disease*; NMS *nonmotor symptoms;* PD *parkinson's disease;* RBD *rapid eye movement behaviour disorder.* GRIN2B *Glutamate Ionotropic Receptor N-methyl-D-aspartate type subunit 2B* DRD *dopamine receptor D1-3.*

3.1. NMS and potential genetic links in EOPD

3.1.1. Cognition and neuropsychiatric symptoms (depression and anxiety)

Some NMS in EOPD appear to specifically segregate to underlying genetic pathophysiology although the links continue to remain tenuous. *GBA1*, apolipoprotein E gene (*APOE*), and alpha-synuclein (*SNCA*) mutations appear to be linked to cognitive decline and although overall rates of cognitive decline are low in EOPD, presence of cognitive impairment in EOPD should prompt a search for these mutations [19–22]. Cognitive decline in *MAPT*, *VPS35*, and *DJ-1* mutation PD patients have mixed results due to small datasets and implications in EOPD are unclear [23–25]. Mood disorders, particular depression and anxiety, are known to be overexpressed in EOPD and can be associated with *SNCA*, *PINK1*, and *DJ-1* mutations while some pathogenic *GBA1* mutation in the EOPD age range are also associated with mood disturbance and anxiety [26,27]. Swan et al. (2016) also reported an association between *GBA1* mutation and anxiety [28]. Furthermore, polymorphisms in the *BDNF* gene [29] and *LRRK2* [30] have been described to be associated with depression and anxiety in PD.

3.1.2. Impulse control disorders (ICD)

Impulse control disorder (ICD) is classed as a neuropsychiatric nonmotor drug induced disorder in PD and can have profound impact on patients' QoL and lead to serious financial and family relationship issues or both. The strongest link is with oral levodopamine agonist (DA) treatment but even levolevodopa can cause ICD [31]. Risk factors include male sex as well as EOPD and therefore, genetic factors which may help predict risk is useful and may in future allow personalisation of treatment.

Among levodopamine receptor genes, a reasonable level of evidence [32–35] suggest that several *SNPs* in the *DRD2* locus as well *AA* genotype of *DRD3* gene are associated with a higher risk of ICD (Table 2). There is weaker evidence suggesting its association with polymorphisms in *GRIN2B* [35,36] and *DRD1* genes [34,35]. Weintraub et al. (2022) have reported weak evidence suggesting a higher association with ICD in four new loci, three of these being *PRKAG2, MEFV*, and *PRKCE* [33]. Other genes suggested are polymorphisms in DBH, ACE and BDNF genes in Russian population [34], as well as *OPRK1* and *HTR2A DDC* genes [32]. Interestingly, in the context of EOPD, some monogenic PD mutations such as *PRKN* [37] and *PINK1* [38] may also show a specific

Table 2
Genetic associations and polymorphisms that have been described in association with or as risk factor for impulse control disorders in Parkinson's Disease including Early Onset Parkinson's Disease cases.

Gene	Association described	Level of evidence
DRD2	Higher risk of ICD in Western population and Asian	+++
GRIN2B	Higher risk of ICD in Western population and Asian	++
DRD1	Higher risk of ICD	++
PRKAG2	Higher risk of ICD	+
MEFV	Higher risk of ICD	+
PRKCE	Higher risk of ICD	+
OPRK1	Higher risk of ICD	+
HTR2A	Higher risk of ICD	+
DDC	Higher risk of ICD	+
DRD3	Higher risk of ICD in Western population and Asian	+
DBH, ACE, BDNF	Higher risk of ICD in Russian population has been described	+
GBA and LRRK2	Higher risk described in PPMI analysis and an observational study	++
Parkin	specific patterns of ICD such as: compulsive shopping, binge eating, and punding/hobbyism	+
PINK1	specific patterns of ICD such as: hypersexuality, compulsive shopping and binge eating	++

+ (low, 1–2 studies); ++ (medium 3–5 studies); +++ (high, >5 studies).
ACE *angiotensin converting enzyme*; BDNF *Brain-derived neurotrophic factor*; DDC *dopa decarboxylase*; DHB *dopamine beta-hydroxylase;* DRD1 *dopamine receptor D1;* DRD2 *dopamine receptor D2;* DRD3 *dopamine receptor D3*; GRIN2B *Glutamate Ionotropic Receptor N-methyl-D-aspartate type subunit 2B;* HTR2A 5-*hydroxytryptamine receptor 2A*; ICD *impulsive compulsive disorder;* MEFV *Familial Mediterranean fever gene*; OPRK1 *opioid receptor kappa 1*; PINK1 *Phosphatase and Tensin Homolog (PTEN) Induced Kinase 1*; PRKAG2 *protein kinase cAMP-dependent type II regulatory subunit beta;* PRKCE *protein kinase c epsilon.* PPMI *Parkinson progression marker initiative*.

Table 3
A range of dominant, recessive, and other genetic mutations may lead to expression of an Early Onset Parkinson's Disease phenotype with preference for specific nonmotor symptoms.

EOPD genetic basis	Specific genetic mutation described	Clinical Association
AD pattern	SNCA	Cognitive decline
AR pattern	ATP13A2 (Kufor Rakeb Syndrome)	Rapid cognitive decline Dementia Optic Atrophy
AR pattern	PRKN	Specific pattern of ICD: Compulsive shopping, Binge eating, Punding, Increased hobbyism Sleep benefit
AR pattern	PINK1	Specific pattern of ICD: Hypersexuality, Compulsive shopping Binge eating
AD pattern (GRIN2B)	GRIN2B DRD1 DRD2	Strong links with ICD Racial variations noted
AD pattern (LRRK2) AR pattern (GBA1)	LRRK2 GBA1 (pathogenic mutations)	Increased rates of ICD
AR pattern	GBA1 pathogenic mutations	Cognitive, decline RBD Dysautonomia
AR pattern	PLA2G6 (PLAN)	Rapid cognitive decline Optic Atrophy
AR pattern (DJ-1) AR pattern (PINK1)	DJ-1 PINK1	Association with pain in PD. PINK1 low back pain described in EOPD.
NA	DRD2 rs2283265 polymorphism	Association with pain in EOPD

AD *autosomal dominant*; AR *autonomic recessive*; ATP1312 *adenosine triphosphate 1312*; DJ1 *deglycase parkinsons disease protein 7*; DRD2 *dopamine receptor D2*. EOPD *early onset Parkinson's disease*; GBA *glucocerebrosidase*; GRIN2B *Glutamate Ionotropic Receptor N-methyl-D-aspartate type subunit 2B;* ICD *Impulse control disorders;* LRRK2 *Leucine-rich repeat kinase 2;* PINK1 *phosphatase and tensin homolog induced kinase 1;* PLA2G6 *phospholipase A2 group 6;* PRKN *parkin*; PLAN PLA2G6 associated *neurodegeneration*; RBD *Rapid eye movement behaviour disorder;* SNCA *alpha synuclein.* NA *not available*.

susceptibility to specific patterns of ICD such as, compulsive shopping, binge eating, punding, and increased hobbyism in the *PRKN* mutations and hypersexuality, compulsive shopping and binge eating in the PINK1 mutations [1] (TTable 3).

In a cross-sectional study of the Parkinson's Progression Marker Initiative (PPMI) cohort, Simuni et al. (2020) examined clinical characteristics of *GBA1* and *LRRK2* carriers compared to matched sporadic PD. and reported that both *GBA1* and *LRRK2* cohorts had higher scores on ICD assessment scales compared to sporadic cases while other neuropsychiatric features were not different [39]. In another comparative observational study, rates of ICD were reported to be significantly higher (52.2 %) compared to a non-GBA1 mutation cohort (13 %) and compulsive shopping, hobbyisms, compulsive eating and hypersexuality were reported most frequently [40].

3.1.3. Pain

Pain is a problematic NMS of EOPD and patients with *PRKN* mutations, which affect younger patients, report painful lower limb dystonia [41]. Unexplained causes of pain are shown to be higher in GBA1 patients (shoulder pain), and *PINK1* mutations in PD [42,43]. *TRPM8* has been established as a risk factor for pain in PD [44] and its relevance to pain in EOPD is currently being explored. Eryilmaz et al. (2020) studied levodopamine D2 and D3 receptor variants linked to motor and aspects of NMS (pain, depression, anxiety, autonomic dysfunction, and hallucinations) of EOPD [45]. They identified three functional single nucleotide polymorphisms (SNPs), *DRD3 rs6280*, *DRD2* rs2283265 and *DRD2* rs1076560, which were genotyped in 128 Turkish EOPD patients and all three SNPs were statistically significantly related to PD pain [45] (Table 3). Specifically, the authors reported that female patient with bilateral PD and *DRD2* rs2283265 polymorphism are likely to be susceptible to pain.

3.1.4. Autonomic dysfunction

Autonomic dysfunction is uncommon in EOPD as evident from the observational cohort studies (Table 1) however, concurrent with cognitive issue a dominant NMS profile of dysautonomia and RBD should prompt screening for pathogenic *GBA1* mutations. Sleep dysfunction is a prodromal feature in EOPD and RBD and insomnia being common complaints, as shown with *GBA1* PD patients having strong RBD manifestations than other groups [46]. In addition, sleep benefit is described well in *PINK1* and *PRKN* mutation EOPD patients [41,47]. *PRKN* presents at a median age of 31 and shows an excellent and robust response to levolevodopa although patients usually develop early motor and nonmotor fluctuations which includes autonomic dysfunction such as hyperhidrosis, anxiety and related tachycardia and sleep benefit [48]. Among the monogenic forms of PD, autosomal dominant (AD) forms of PD due to SNCA mutations and some specific mutations in *LRRK2* gene have shown higher frequency of dysautonomia when compared to sporadic PD or *LRRK2* non-carriers, with high level of evidence [49–54]. But penetration of *LRRK2* gene in EOPD is low and therefore it is unlikely that these mutations would be of any significant clinical relevance in EOPD.

No other genetic association has been described in EOPD cases which link genetic mutations to other non-motor symptoms such as apathy, sexual dysfunction (apart from related ICD) or body weight.

4. Juvenile onset PD and EOPD overlap

Juvenile parkinsonism (JP) usually has an onset at less than 20 years-of-age and can be caused by a range of genetic and other aetiologies such

as, drug induced, toxin induced, autoimmune, metabolic, and structural. Genetic causes could be, autosomal recessive such as, *parkin*, *PINK* 1, *DJ-1, AD* ones such as SNCA, levodopa responsive dystonia, rapid onset dystonia parkinsonism, and *X*-linked such as, *DYT-PARK-TAF1* (Lubag), neuronal brain iron accumulation (NBIA) syndromes as well as *RAB39B* [68]. Some other monogenic mutations, which usually map with EOP-ism can also present as EOPD, these include *PLA2G6* mutations, *SNCA*, and *ATP13A2*. Rarely *PLA2G6* mutation, which usually presents between 3rd to 4th decade, may present with levolevodopa responsive PD and depression or anxiety [69], although atypical features for EOPD, such as rapid cognitive decline and optic atrophy, occurs as a red flag. *ATP13A2* mutations can present at a mean age of 24 years and develop optic atrophy and rapid cognitive decline, unusual for a typical EOPD spectrum. The *SNCA* mutation can present between the 2nd-7th decade and once aging the Parkinsonism is soon complicated by rapid cognitive decline and neuropsychiatric features [22].

Symptoms are varied and often include motor symptoms such as dystonia as well as atypical features such as cognitive impairment, neuropsychiatric issues, seizures, and variable levolevodopa response. Muthane et al. (1994) performed a comparative study of EOPD versus JOPD and reported that while all EOPD cases had rest tremors, 15 % of JOPD cases had no rest tremor and dystonia (43 %) and autonomic symptoms (42 %) were more frequent in JOPD compared to EOPD (tremor 9 %, autonomic 17 %) [67]. No other differences were reported. Others have also reported higher rates of dystonia and dyskinesias in EOPD [3,70].

Specifically, in terms of differential diagnosis, one may also need to consider metabolic conditions such as, Wilson's disease (common in India, Middle East regions), spinocerebellar ataxias SCAs (especially SCA1, 2, and 3), as well as hereditary spastic paraplegias, mitochondrial and metabolic disorders, and infection related parkinsonism but a detailed discussion is beyond the scope of this paper focused on NMS and EOPD.

5. NMS profile in EOPD patients

While NMS profile have been extensively reported in sporadic idiopathic middle onset PD (MOPD) or LOPD studies in typical EOPD using validated holistic tools, such as the PD NMS scale, are scarce. Using Pubmed searches, searches from the PD Nonmotor Group (PDNMG), as well as Google scholar, we identified a handful of papers starting from 2013, which addressed NMS in EOPD in comparative or controlled studies (Table 1).

Numerous studies have elucidated that PD patients manifest distinct clinical NMS depending on their age at onset. In the EOPD patients' group, cognitive impairment appears to be less prevalent compared to LOPD [55,61,63,65] however, there are some divergent findings. EOPD patients have significantly higher mini mental state examination (MMSE) scores and less frequently experience depressive disorders (lower Hamilton Depression Rating Scale scores). In one study by Spica et al. (2013), the anxiety rate was reported as similar between both the EOPD and LOPD groups [55]. However, other studies suggest high anxiety rates in EOPD [59]. The authors report the only NMS more prevalent in EOPD were restless legs and sweating, although these findings might be associated with drug effects.

On the other hand, Kim et al. (2020) found that in EOPD patients exhibited higher Montreal cognitive Assessment (MoCA) scores, along with increased anxiety levels (measured by State-Trait Anxiety Inventory), compared to both MOPD and LOPD groups [59]. Scale of Parkinson's Assessment (SCOPA) autonomic function (AUT) scores, particularly in gastrointestinal, urinary, and sexual sub scores, were lower in the EOPD group compared to the LOPD group pointing towards lesser autonomic disturbances in EOPD patients [59]. Additionally, the mean caudate and putamen levodopaminergic transporter binding ratios were higher in the EOPD group than in the other groups [59]. Mehanna et al. (2022) reported doubling of rates of depression in EOPD compared to late onset PD and in another study, Knipe et al. (2011) reported that depression, worse emotional well-being, and poorer QoL was more prevalent in EOPD [57,71].

De et al. (2023) reported that EOPD patients experience significantly fewer cardiovascular problems, including falls, memory, and attention issues, as well as perceptual problems and hallucinations, when compared to MOPD and LOPD. Furthermore, miscellaneous symptoms such as taste, smell, weight, and sweating issues were significantly less frequent in EOPD patients [62].

In turn, it has been reported that ICD are much more common in EOPD patients than in healthy controls, and it might be due to abnormal sensitivity to levodopamine agonist intake, concomitant depression, leading to a lower QoL [58,64].

In the EOPD cohort, sexual dysfunction (SD) is more common in patients than in the general population [60]. All sexuality domains, including libido, erectile function, and ejaculation, were reduced in male EOPD patients. Similarly, SD was more prevalent in EOPD woman than in the general population along with decreased lubrication and increased pain during intercourse. Sexual dissatisfaction was more prevalent in male EOPD patients compared to the general population. Among EOPD patients, male gender and urinary dysfunction were linked to sexual dysfunction and dissatisfaction. SD was also associated with depression [60].

Of interest, Zhou et al. (2013) conduct a study suggesting that EOPD was considered as protective factor against loss of interest and concentration compared to LOPD. EOPD patients also demonstrated better scores in MMSE and were less likely to experience impaired taste or smell. Additionally, they reported EOPD patients to have significantly less dribbling and constipation, and did not present with sleep disturbances, when compared to LOPD patients [56]. However, Bovenzi et al. (2023) demonstrated that at the onset of EOPD, patients frequently suffer from RBD and constipation, often occurring together [64].

Hoang et al. (2023) demonstrated that pain might be more prevalent and severe in EOPD patients than previously appreciated. In their study, 79.3 % of patients reported pain. The most common subtype of pain was musculoskeletal (70.1 %), followed by nocturnal (43.9 %), radicular (43.0 %), chronic (42.1 %), fluctuation-related (34.6 %) and orofacial pain (16.8 %) [63]. Majority of patients (74.8 %) experienced more than one type of pain. Those with depression and higher Hoehn and Yahr (H&Y) stages (3–5) had significantly higher mean scores on the KPPS compared to patients without depression and at lower H&Y stages (1–2) [63].

Patwardhan et al. (2024) reported that in an Indian cohort of EOPD, the patients demonstrated a high overall NMS burden comparing to healthy control. In addition presence of ICD and excessive day time sleepiness were found to significantly influence the QoL of these patients [65].

Reports from EOPD population in Greece, report autonomic impairment, constipation together with urinary symptoms (urgency, frequency and nocturia) as being less frequent compared to LOPD patients [61]. It has been also demonstrated that dementia tended to be more common in MOPD and LOPD subgroup compared to EOPD, but this difference was not statistically significant [61].

Overall, these studies (Table 1) do report some contradictory finding possibly related to varying cohorts, methodology, and lack of validated instruments in some. However, a broad unifying picture of the nonmotor profile in EOPD does emerge (Fig. 2).

Based on the above studies and clinical expert experience, we propose a nonmotor profile in PD (Fig. 2). Key factors include (a) there to be a relatively low rate of cognitive impairment, while (b) there are higher rates of anxiety, sexual dysfunction, pain as well as impulse control disorders. The data on depression is controversial and contradictory and may reflect the difficulties of living with PD at an expected fit and active phase of life.

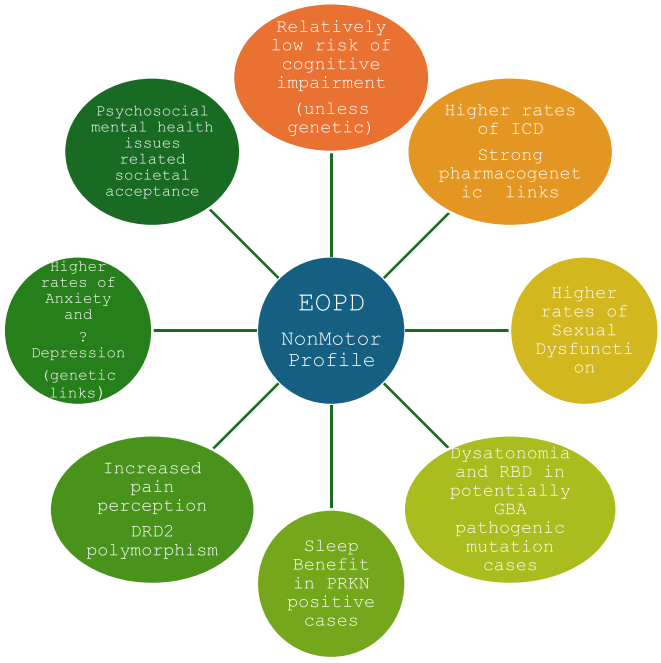

Fig. 2. A proposed nonmotor profile in EOPD
DRD2 *dopamine receptor D2;* EOPD *early onset Parkinson's disease;* GBA *Glucocerebrosidase;* PRKN *Parkin;* ICD *impulsive compulsive disorder;* RBD *rapid eye movement behaviour disorders*.

6. Nonmotor subtypes and EOPD

Recent work suggests the emergence and phenotypic expression of NMS dominant phenotypes, originally termed the nonmotor subtypes of PD [13,72]. More recently, these have been defined further and specific cholinergic, noradrenergic, and Park sleep subtypes have been described [73,74]. While the cholinergic subtype, which carries a higher risk of progression to dementia, is more prevalent in older and LOPD, the Park-sleep and noradrenergic subtypes can occur in EOPD as well as late onset PD. In terms of therapeutic potential there is a need and role of subtype specific personalised therapies, such as avoiding levodopamine D3 receptor active levodopamine agonists in the park-sleep subtype [74].

Little is also known about the progression pattern in EOPD and whether there is any real difference from the late onset PD. In one study, YOPD/EOPD are reported to have had a mean decrease of 0.22 fewer points per year in the MoCA scores ($p = 0.002$) than the MOPD group while other non-motor progression did not differ among the groups [59].

7. EOPD versus LOPD

There is currently no formal distinction between the clinical phenotype of EOPD and the more usual LOPD, which usually peaks around the ages of 60–80 yrs. There are geographical peculiarities with reports of EOPD being more frequent for instance from India as well as UAE [66,75]. Prasad et al. (2023) reported that that the average age at onset of PD in India was 51.03 ± 11.32 years (coming into the range for EOPD) and 45.06 % of a cohort of 2035 patients had an average age of onset between 22 and 49 years [66].

8. Challenges related to nonmotor profile and diagnosis of EOPD

From a nonmotor angle, as discussed above, there are specific challenges in EOPD. ICD, neuropsychiatric issues such as, depression, anxiety, pain, and a range of SD can occur in EOPD. These NMS are less prevalent in older PD, where cognitive issues, apathy, dysautonomia, and psychosis appear to be commoner. ICDs specifically pose a significant psychosocial and management dilemma in EOPD as reward seeking behaviours such as, hypersexuality, compulsive gambling, reckless spending, and compulsive shopping are more likely to occur with the use of levodopamine agonists and culturally sensitive and bespoke consultation with the patient is required. This is because patients may not want to share such information and in some societies these ICD related NMS could be socially stigmatising, as well as culturally inappropriate. Genetics may play a part, as previously alluded to, and in the study by Prasad et al. (2022), nineteen percent of the *GBA1* cohort had signs and symptoms suggestive of ICD and this observation is in line with a report that patients with PD due to GBA1 mutation may carry a higher lifetime prevalence of ICD [40].

Additional, psychosocial challenges of EOPD occur as the longer disease duration in EOPD, longer lived experience of living with PD. social interaction related difficulties (which may be specifically relevant to young age), concern and guilt about caregiver burden can lead to significant depression and anxiety and behavioural issues. Career and work issues also remain a significant factor that may affect mental health in EOPD [6].

9. Secondary causes of EOPD

There are many causes of secondary parkinsonism and drug-induced parkinsonism (linked to the use of levodopamine blocking drugs, levodopamine or calcium antagonists, sodium valproate) and vascular parkinsonism are common forms of secondary parkinsonism and can also present in the EOPD group and needs exclusion. Such patients often have a symmetric onset presentation and may lack classical rest tremor. A recent study has suggested that in EOPD, once genetic causes have been excluded, there may be a link of sport related head trauma and EOPD [76]. Such patients may have hyposmia, cognitive issues, as well as neuropsychiatric problems, and further work is required to investigate the role of this potential risk factor.

10. Therapeutic advances for EOPD

Symptomatic levodopamine replacement therapies as well as lifestyle based non-pharmacological interventions such as, physical activity, dance, and tai chi may have significant beneficial effect on some NMS in EOPD such as depression and pain. Levodopamine replacement therapies remain the cornerstone of treatment, but caution is required in relation to the use of levodopamine agonists use specially in EOPD cases with previous history of addiction, gambling or hypersexuality. Diagnosis of EOPD also must be given in an extremely sensitive and culturally accepTable manner given the challenges of living with EOPD in relatively young age. Neuroprotective trials thus far have failed but remain of crucial importance in EOPD should there be a successful report from many such trials currently under way. Genomic precision medicine based personalised medicine such as the use of repurposed drug Ambroxol for GBA1 positive cases in EOPD may be of great importance in future as potentially cognitive issues can be addressed and even prevented [77]. A recent trial of structured ballet provided by trained instructors from English National Ballet in EOPD and LOPD reported benefits in several NMS such as anxiety, depression, sleep problems and pain [78]. A beneficial effect of transcranial direct current stimulation based non-invasive neuromodulation in 10 PD patients have been reported compared to sham stimulation where patients reported benefit in nonmotor symptoms scale total score as well as item 2 of sleep/fatigue [79]. STEM-PD is multicentre clinical trial which is investigating sham versus active caloric vestibular stimulation mediated brainstem neuromodulation, which may also benefit many NMS in PD (NCT04797611).

11. Conclusions

EOPD possibly constitutes about 10–20 % of all PD cases and form a

group of PD cases usually aged between 21 and 50 years as recently defined by a dedicated task force. Global prevalence varies and data from India suggest that rates of EOPD could be as high as 40 % and a lower age of onset has also been reported from Middle East. The clinical phenotype may be like late onset or older onset PD, but asymmetry remains pronounced and there is a stronger genetic footprint in EOPD apart from a slightly different motor and nonmotor footprint which includes higher rates of dystonia, pain, neuropsychiatric symptoms, and genetically linked NMS such as cognitive issues in *GBA1* positive cases. There are major challenges faced by EOPD patients in terms of employment, sexual health, as well as professional and caregiver issues while the profile of NMS seems different to typical LOPD. Anxiety and depression are common symptoms and lead to poor QoL. Pain may also be dominant and may also be linked to DRD2 receptor polymorphism, while cognitive dysfunction, sleep problems as well as dysautonomia seems much less frequent but could occur in genetic cases of EOPD. Sexual health and sexual dysfunction appear common in EOPD and may be linked to levodopamine agonist linked ICD which brings major clinical and societal challenges. Recognition of the differences in clinical presentation of EOPD is important for devising and delivering modern multifaceted personalised care.

CRediT authorship contribution statement

Karolina Poplawska-Domaszewicz: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Mubasher A. Qamar:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Cristian Falup Pecurariu:** Writing – review & editing. **K Ray Chaudhuri:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Parkinson Foundation Centre of Excellence Kings College Hospital, London, UK.

References

[1] N. Titova, K.R. Chaudhuri, Personalized medicine and nonmotor symptoms in Parkinson's disease, Int. Rev. Neurobiol. 134 (2017) 1257–1281.
[2] L.M. de Lau, M.M. Breteler, Epidemiology of Parkinson's disease, Lancet Neurol. 5 (6) (2006) 525–535.
[3] L.I. Golbe, Young-onset Parkinson's disease: a clinical review, Neurology 41 (1991) 168–173, 2 Pt 1).
[4] P. Ylikotila, T. Tiirikka, J.S. Moilanen, H. Kaariainen, R. Marttila, K. Majamaa, Epidemiology of early-onset Parkinson's disease in Finland, Parkinsonism Relat Disord 21 (8) (2015) 938–942.
[5] R. Mehanna, K. Smilowska, J. Fleisher, B. Post, T. Hatano, M.E. Pimentel Piemonte, K.R. Kumar, V. McConvey, B. Zhang, E.K. Tan, R. Savica, P. International, D. Movement Disorder Society Task Force on Early Onset Parkinson's, Age cutoff for early-onset Parkinson's disease: recommendations from the international Parkinson and movement disorder society task force on early onset Parkinson's disease, Mov Disord Clin Pract 9 (7) (2022) 869–878.
[6] S. Prasad, P. Kumar Pal, Early onset Parkinson's disease in India: challenges in diagnosis and management. https://www.worldneurology.com/post/early-onset-parkinson-s-disease-in-india-challenges-in-diagnosis-and-management.2024, 2023.
[7] G.M. Riboldi, E. Frattini, E. Monfrini, S.J. Frucht, A. Di Fonzo, A practical approach to early-onset parkinsonism, J. Parkinsons Dis. 12 (1) (2022) 1–26.
[8] K.R. Chaudhuri, Progression and biomarkers for Parkinson disease: merging motor with nonmotor symptoms, Neurology 87 (2) (2016) 128–129.
[9] K.R. Chaudhuri, A. Sauerbier, Parkinson disease. Unravelling the nonmotor mysteries of Parkinson disease, Nat. Rev. Neurol. 12 (1) (2016) 10–11.
[10] N. Titova, M.A. Qamar, K.R. Chaudhuri, The nonmotor features of Parkinson's disease, Int. Rev. Neurobiol. 132 (2017) 33–54.
[11] K.M. Prakash, N.V. Nadkarni, W.K. Lye, M.H. Yong, E.K. Tan, The impact of non-motor symptoms on the quality of life of Parkinson's disease patients: a longitudinal study, Eur. J. Neurol. 23 (5) (2016) 854–860.
[12] D.J. van Wamelen, A. Sauerbier, V. Leta, C. Rodriguez-Blazquez, C. Falup-Pecurariu, M. Rodriguez-Violante, A. Rizos, Y. Tsuboi, V. Metta, R. Bhidayasiri, K. Bhattacharya, R. Borgohain, L.K. Prashanth, R. Rosales, S. Lewis, V. Fung, M. Behari, V. Goyal, A. Kishore, S.P. Lloret, P. Martinez-Martin, K.R. Chaudhuri, Cross-sectional analysis of the Parkinson's disease Non-motor International Longitudinal Study baseline non-motor characteristics, geographical distribution and impact on quality of life, Sci. Rep. 11 (1) (2021) 9611.
[13] A. Sauerbier, P. Jenner, A. Todorova, K.R. Chaudhuri, Non motor subtypes and Parkinson's disease, Parkinsonism Relat Disord 22 (Suppl 1) (2016) S41–S46.
[14] R.B. Postuma, D. Berg, Advances in markers of prodromal Parkinson disease, Nat. Rev. Neurol. 12 (11) (2016) 622–634.
[15] D. Berg, J. Godau, K. Seppi, S. Behnke, I. Liepelt-Scarfone, S. Lerche, H. Stockner, A. Gaenslen, P. Mahlknecht, H. Huber, K. Srulijes, J. Klenk, K. Fassbender, W. Maetzler, W. Poewe, P.s. group, The PRIPS study: screening battery for subjects at risk for Parkinson's disease, Eur. J. Neurol. 20 (1) (2013) 102–108.
[16] K. Brockmann, K. Srulijes, A.-K. Hauser, C. Schulte, I. Csoti, T. Gasser, D. Berg, GBA1-associated PD presents with nonmotor characteristics, Neurology 77 (3) (2011) 276–280.
[17] K. Brockmann, K. Srulijes, S. Pflederer, A.K. Hauser, C. Schulte, W. Maetzler, T. Gasser, D. Berg, GBA1-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study, Mov. Disord. 30 (3) (2015) 407–411.
[18] A. Kolicheski, P. Turcano, N. Tamvaka, P.J. McLean, W. Springer, R. Savica, O. A. Ross, Early-onset Parkinson's disease: creating the right environment for a genetic disorder, J. Parkinsons Dis. 12 (8) (2022) 2353–2367.
[19] L. Oftedal, J. Maple-Grodem, I. Dalen, O.B. Tysnes, K.F. Pedersen, G. Alves, J. Lange, Association of CSF glucocerebrosidase activity with the risk of incident dementia in patients with Parkinson disease, Neurology 100 (4) (2023) e388–e395.
[20] D. Aarsland, L. Batzu, G.M. Halliday, G.J. Geurtsen, C. Ballard, K. Ray Chaudhuri, D. Weintraub, Parkinson disease-associated cognitive impairment, Nat Rev Dis Primers 7 (1) (2021) 47.
[21] N. Pankratz, L. Byder, C. Halter, A. Rudolph, C.W. Shults, P.M. Conneally, T. Foroud, W.C. Nichols, Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia, Mov. Disord. 21 (1) (2006) 45–49.
[22] R.N. Duan, G.Y. Liu, Y.L. Han, P.Z. Li, B.H. Zhang, Y.M. Liu, Characterization of SNCA multiplication in Parkinson's disease: 2 new cases and evaluation of the literature, Mov Disord Clin Pract 10 (10) (2023) 1536–1541.
[23] K.C. Paul, R. Rausch, M.M. Creek, J.S. Sinsheimer, J.M. Bronstein, Y. Bordelon, B. Ritz, APOE, MAPT, and COMT and Parkinson's disease susceptibility and cognitive symptom progression, J. Parkinsons Dis. 6 (2) (2016) 349–359.
[24] C. Vilarino-Guell, C. Wider, O.A. Ross, J.C. Dachsel, J.M. Kachergus, S.J. Lincoln, A.I. Soto-Ortolaza, S.A. Cobb, G.J. Wilhoite, J.A. Bacon, B. Behrouz, H.L. Melrose, E. Hentati, A. Puschmann, D.M. Evans, E. Conibear, W.W. Wasserman, J.O. Aasly, P.R. Burkhard, R. Djaldetti, J. Ghika, F. Hentati, A. Krygowska-Wajs, T. Lynch, E. Melamed, A. Rajput, A.H. Rajput, A. Solida, R.M. Wu, R.J. Uitti, Z.K. Wszolek, F. Vingerhoets, M.J. Farrer, VPS35 mutations in Parkinson disease, Am. J. Hum. Genet. 89 (1) (2011) 162–167.
[25] C. Klein, A. Djarmati, K. Hedrich, N. Schafer, C. Scaglione, R. Marchese, N. Kock, B. Schule, A. Hiller, T. Lohnau, S. Winkler, K. Wiegers, R. Hering, P. Bauer, O. Riess, G. Abbruzzese, P. Martinelli, P.P. Pramstaller, PINK1, Parkin, and DJ-1 mutations in Italian patients with early-onset parkinsonism, Eur. J. Hum. Genet. 13 (9) (2005) 1086–1093.
[26] A. Thaler, N. Bregman, T. Gurevich, T. Shiner, Y. Dror, O. Zmira, Z. Gan-Or, A. Bar-Shira, M. Gana-Weisz, A. Orr-Urtreger, N. Giladi, A. Mirelman, Parkinson's disease phenotype is influenced by the severity of the mutations in the GBA1 gene, Parkinsonism Relat Disord 55 (2018) 45–49.
[27] K. Kalinderi, V. Papaliagkas, L. Fidani, Current genetic data on depression and anxiety in Parkinson's disease patients, Parkinsonism Relat Disord 118 (2024) 105922.
[28] M. Swan, N. Doan, R.A. Ortega, M. Barrett, W. Nichols, L. Ozelius, J. Soto-Valencia, S. Boschung, A. Deik, H. Sarva, J. Cabassa, B. Johannes, D. Raymond, K. Marder, N. Giladi, J. Miravite, W. Severt, R. Sachdev, V. Shanker, S. Bressman, R. Saunders-Pullman, Neuropsychiatric characteristics of GBA1-associated Parkinson disease, J. Neurol. Sci. 370 (2016) 63–69.
[29] F.C. Cagni, C. Campelo, D.G. Coimbra, M.R. Barbosa, L.G.O. Junior, A.B.S. Neto, A. M. Ribeiro, C.O.G. Junior, T. Gomes de Andrade, R.H. Silva, Association of BDNF Val66MET polymorphism with Parkinson's disease and depression and anxiety symptoms, J. Neuropsychiatry Clin. Neurosci. 29 (2) (2017) 142–147.
[30] A. Mirelman, R.N. Alcalay, R. Saunders-Pullman, K. Yasinovsky, A. Thaler, T. Gurevich, H. Mejia-Santana, D. Raymond, M. Gana-Weisz, A. Bar-Shira, L. Ozelius, L. Clark, A. Orr-Urtreger, S. Bressman, K. Marder, N. Giladi, L. A. consortium, Nonmotor symptoms in healthy Ashkenazi Jewish carriers of the G2019S mutation in the LRRK2 gene, Mov. Disord. 30 (7) (2015) 981–986.
[31] D. Weintraub, J. Koester, M.N. Potenza, A.D. Siderowf, M. Stacy, V. Voon, J. Whetteckey, G.R. Wunderlich, A.E. Lang, Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients, Arch. Neurol. 67 (5) (2010) 589–595.
[32] J. Kraemmer, K. Smith, D. Weintraub, V. Guillemot, M.A. Nalls, F. Cormier-Dequaire, I. Moszer, A. Brice, A.B. Singleton, J.C. Corvol, Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 87 (10) (2016) 1106–1111.

[33] D. Weintraub, M. Posavi, P. Fontanillas, T.F. Tropea, E. Mamikonyan, E. Suh, J. Q. Trojanowski, P. Cannon, V.M. Van Deerlin, T. andMe Research, A.S. Chen-Plotkin, Genetic prediction of impulse control disorders in Parkinson's disease, Ann Clin Transl Neurol 9 (7) (2022) 936–949.
[34] A. Fedosova, N. Titova, Z. Kokaeva, N. Shipilova, E. Katunina, E. Klimov, Genetic markers as risk factors for the development of impulsive-compulsive behaviors in patients with Parkinson's disease receiving levodopaminergic therapy, J Pers Med 11 (12) (2021).
[35] S. Zainal Abidin, E.L. Tan, S.C. Chan, A. Jaafar, A.X. Lee, M.H. Abd Hamid, N. A. Abdul Murad, N.F. Pakarul Razy, S. Azmin, A. Ahmad Annuar, S.Y. Lim, P. S. Cheah, K.H. Ling, N. Mohamed Ibrahim, DRD and GRIN2B polymorphisms and their association with the development of impulse control behaviour among Malaysian Parkinson's disease patients, BMC Neurol. 15 (2015) 59.
[36] J.Y. Lee, E.K. Lee, S.S. Park, J.Y. Lim, H.J. Kim, J.S. Kim, B.S. Jeon, Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease, Mov. Disord. 24 (12) (2009) 1803–1810.
[37] F. Morgante, A. Fasano, M. Ginevrino, S. Petrucci, L. Ricciardi, F. Bove, C. Criscuolo, M. Moccia, A. De Rosa, C. Sorbera, A.R. Bentivoglio, P. Barone, G. De Michele, M.T. Pellecchia, E.M. Valente, Impulsive-compulsive behaviors in parkin-associated Parkinson disease, Neurology 87 (14) (2016) 1436–1441.
[38] L. Ricciardi, S. Petrucci, A. Guidubaldi, T. Ialongo, L. Serra, A. Ferraris, B. Spano, M. Bozzali, E.M. Valente, A.R. Bentivoglio, Phenotypic variability of PINK1 expression: 12 Years' clinical follow-up of two Italian families, Mov. Disord. 29 (12) (2014) 1561–1566.
[39] T. Simuni, M.C. Brumm, L. Uribe, C. Caspell-Garcia, C.S. Coffey, A. Siderowf, R. N. Alcalay, J.Q. Trojanowski, L.M. Shaw, J. Seibyl, A. Singleton, A.W. Toga, D. Galasko, T. Foroud, K. Nudelman, D. Tosun-Turgut, K. Poston, D. Weintraub, B. Mollenhauer, C.M. Tanner, K. Kieburtz, L.M. Chahine, A. Reimer, S. Hutten, S. Bressman, K. Marek, I. Parkinson's, Progression markers initiative, clinical and levodopamine transporter imaging characteristics of leucine rich repeat kinase 2 (LRRK2) and glucosylceramidase beta (GBA1) Parkinson's disease participants in the Parkinson's progression markers initiative: a cross-sectional study, Mov. Disord. 35 (5) (2020) 833–844.
[40] P. Amami, T. De Santis, F. Invernizzi, B. Garavaglia, A. Albanese, Impulse control behavior in GBA1-mutated parkinsonian patients, J. Neurol. Sci. 421 (2021) 117291.
[41] C.B. Lucking, A. Durr, V. Bonifati, J. Vaughan, G. De Michele, T. Gasser, B. S. Harhangi, G. Meco, P. Denefle, N.W. Wood, Y. Agid, A. Brice, G. French, Parkinson's disease genetics study, D. European consortium on genetic susceptibility in Parkinson's, association between early-onset Parkinson's disease and mutations in the PRKNgene, N. Engl. J. Med. 342 (21) (2000) 1560–1567.
[42] N. Kresojevic, M. Jankovic, I. Petrovic, K.R. Kumar, N. Dragasevic, V. Dobricic, I. Novakovic, M. Svetel, C. Klein, T. Pekmezovic, V.S. Kostic, Presenting symptoms of GBA1-related Parkinson's disease, Parkinsonism Relat Disord 21 (7) (2015) 804–807.
[43] J. Gierthmuhlen, F. Lienau, R. Maag, J.M. Hagenah, G. Deuschl, E. Fritzer, C. Klein, R. Baron, C. Helmchen, Somatosensory processing in a German family with PINK1 mutations: its potential role in Parkinson disease, J. Neurol. Neurosurg. Psychiatry 80 (5) (2009) 571–574.
[44] N.M. Williams, L. Hubbard, C. Sandor, C. Webber, H. Hendry, M. Lawton, C. Carroll, K.R. Chaudhuri, H. Morris, M.T. Hu, D.G. Grosset, C. Kobylecki, M. Silverdale, U.K.P.s.P. Study, Genome-wide association study of pain in Parkinson's disease implicates TRPM8 as a risk factor, Mov. Disord. 35 (4) (2020) 705–707.
[45] I.E. Eryilmaz, S. Erer, M. Zarifoglu, U. Egeli, E. Karakus, B. Yurdacan, G. Cecener, B. Tunca, B. Colakoglu, A. Bora Tokcaer, E. Saka, M. Demirkiran, C. Akbostanci, O. Dogu, H. Kaleagasi, G. Kenangil, R. Cakmur, B. Elibol, Contribution of functional levodopamine D2 and D3 receptor variants to motor and non-motor symptoms of early onset Parkinson's disease, Clin. Neurol. Neurosurg. 199 (2020) 106257.
[46] M. Avenali, M. Toffoli, S. Mullin, A. McNeil, D.A. Hughes, A. Mehta, F. Blandini, A. H.V. Schapira, Evolution of prodromal parkinsonian features in a cohort of GBA1 mutation-positive individuals: a 6-year longitudinal study, J. Neurol. Neurosurg. Psychiatry 90 (10) (2019) 1091–1097.
[47] T. Kitada, S. Asakawa, N. Hattori, H. Matsumine, Y. Yamamura, S. Minoshima, M. Yokochi, Y. Mizuno, N. Shimizu, Mutations in the PRKNgene cause autosomal recessive juvenile parkinsonism, Nature 392 (6676) (1998) 605–608.
[48] N.L. Khan, E. Graham, P. Critchley, A.E. Schrag, N.W. Wood, A.J. Lees, K.P. Bhatia, N. Quinn, PRKNdisease: a phenotypic study of a large case series, Brain 126 (Pt 6) (2003) 1279–1292.
[49] V. Chelban, E. Vichayanrat, L. Schottlaende, V. Iodice, H. Houlden, Autonomic dysfunction in genetic forms of synucleinopathies, Mov. Disord. 33 (3) (2018) 359–371.
[50] B. Tijero, J.C. Gomez Esteban, J. Somme, V. Llorens, E. Lezcano, A. Martinez, T. Rodriguez, K. Berganzo, J.J. Zarranz, Autonomic dysfunction in parkinsonian LRRK2 mutation carriers, Parkinsonism Relat Disord 19 (10) (2013) 906–909.
[51] A. Nasri, I. Kacem, N. Farhat, A. Gharbi, S. Sakka, A. Souissi, S. Zidi, M. Damak, M. Bendjebara, A. Gargouri, C. Mhiri, R. Gouider, Heart rate variability and sympathetic skin response for the assessment of autonomic dysfunction in leucine-rich repeat kinase 2 associated Parkinson's disease, Neurophysiol. Clin. 52 (1) (2022) 81–93.
[52] N.P. Visanji, G.S. Bhudhikanok, T.A. Mestre, T. Ghate, K. Udupa, A. AlDakheel, B. S. Connolly, C. Gasca-Salas, D.S. Kern, J. Jain, E.J. Slow, A. Faust-Socher, S. Kim, R. Azhu Valappil, F. Kausar, E. Rogaeva, J. William Langston, C.M. Tanner, B. Schule, A.E. Lang, S.M. Goldman, C. Marras, Heart rate variability in leucine-rich repeat kinase 2-associated Parkinson's disease, Mov. Disord. 32 (4) (2017) 610–614.
[53] C. Carricarte Naranjo, C. Marras, N.P. Visanji, D.J. Cornforth, L. Sanchez-Rodriguez, B. Schule, S.M. Goldman, M. Estevez, P.K. Stein, A.E. Lang, H.F. Jelinek, A. Machado, Increased markers of cardiac vagal activity in leucine-rich repeat kinase 2-associated Parkinson's disease, Clin. Auton. Res. 29 (6) (2019) 603–614.
[54] C. Pont-Sunyer, E. Tolosa, C. Caspell-Garcia, C. Coffey, R.N. Alcalay, P. Chan, J. E. Duda, M. Facheris, R. Fernandez-Santiago, K. Marek, F. Lomena, C. Marras, E. Mondragon, R. Saunders-Pullman, B. Waro, L.C. Consortium, The prodromal phase of leucine-rich repeat kinase 2-associated Parkinson disease: clinical and imaging Studies, Mov. Disord. 32 (5) (2017) 726–738.
[55] V. Spica, T. Pekmezovic, M. Svetel, V.S. Kostic, Prevalence of non-motor symptoms in young-onset versus late-onset Parkinson's disease, J. Neurol. 260 (1) (2013) 131–137.
[56] M.Z. Zhou, J. Gan, Y.R. Wei, X.Y. Ren, W. Chen, Z.G. Liu, The association between non-motor symptoms in Parkinson's disease and age at onset, Clin. Neurol. Neurosurg. 115 (10) (2013) 2103–2107.
[57] R. Mehanna, S. Moore, J.G. Hou, A.I. Sarwar, E.C. Lai, Comparing clinical features of young onset, middle onset and late onset Parkinson's disease, Parkinsonism Relat Disord 20 (5) (2014) 530–534.
[58] L. Vela, J.C. Martinez Castrillo, P. Garcia Ruiz, C. Gasca-Salas, Y. Macias Macias, E. Perez Fernandez, I. Ybot, E. Lopez Valdes, M.M. Kurtis, I.J. Posada Rodriguez, M. Mata, C. Ruiz Huete, M. Eimil, C. Borrue, J. Del Val, L. Lopez-Manzanares, A. Rojo Sebastian, R. Marasescu, The high prevalence of impulse control behaviors in patients with early-onset Parkinson's disease: a cross-sectional multicenter study, J. Neurol. Sci. 368 (2016) 150–154.
[59] R. Kim, J.H. Shin, S. Park, H.J. Kim, B. Jeon, Longitudinal evolution of non-motor symptoms according to age at onset in early Parkinson's disease, J. Neurol. Sci. 418 (2020) 117157.
[60] L. Vela-Desojo, D. Urso, M. Kurtis-Urra, P.J. Garcia-Ruiz, E. Perez-Fernandez, E. Lopez-Valdes, I. Posada-Rodriguez, I. Ybot-Gorrin, L. Lopez-Manzanares, M. Mata, C. Borrue, C. Ruiz-Huete, M. Del Valle, J.C. Martinez-Castrillo, Sexual dysfunction in early-onset Parkinson's disease: a cross-sectional, multicenter study, J. Parkinsons Dis. 10 (4) (2020) 1621–1629.
[61] E. Angelopoulou, M. Bozi, A.M. Simitsi, C. Koros, R. Antonelou, N. Papagiannakis, M. Maniati, D. Poula, M. Stamelou, D.K. Vassilatis, I. Michalopoulos, S. Geronikolou, N. Scarmeas, L. Stefanis, Clinical differences between early-onset and mid-and-late-onset Parkinson's disease: data analysis of the Hellenic Biobank of Parkinson's disease, J. Neurol. Sci. 442 (2022) 120405.
[62] L. De Carolis, S. Galli, E. Bianchini, D. Rinaldi, M. Raju, B. Calio, M. Alborghetti, F. E. Pontieri, Age at onset influences progression of motor and non-motor symptoms during the early stage of Parkinson's disease: a monocentric retrospective study, Brain Sci. 13 (2) (2023).
[63] D.T. Hoang, F. Xing, T.D. Nguyen, T.D. Nguyen, T.N. Tran, S.D. Nhu, Q.H. Nguyen, H.T. Nguyen, U.T. Hoang, Q.V. Than, D. Truong, Pain is common in early onset Parkinson's disease and pain severity is associated with age and worsening of motor and non-motor symptoms, J. Neurol. Sci. 455 (2023) 122784.
[64] R. Bovenzi, M. Conti, G.R. Degoli, R. Cerroni, C. Simonetta, C. Liguori, C. Salimei, A. Pisani, M. Pierantozzi, A. Stefani, N.B. Mercuri, T. Schirinzi, Shaping the course of early-onset Parkinson's disease: insights from a longitudinal cohort, Neurol. Sci. 44 (9) (2023) 3151–3159.
[65] A. Patwardhan, N. Kamble, A. Bhattacharya, V. Holla, R. Yadav, P.K. Pal, Impact of non-motor symptoms on quality of life in patients with early-onset Parkinson's disease, Can. J. Neurol. Sci. (2024) 1–10.
[66] S. Prasad, K. Rakesh, N. Kamble, V.V. Holla, P. Mailankody, A. Lenka, R. M. Naduthota, A. Stezin, R. Mahale, R. Yadav, P.K. Pal, Early onset of Parkinson's disease in India: complicating the conundrum, Parkinsonism Relat Disord 105 (2022) 111–113.
[67] U.B. Muthane, H.S. Swamy, P. Satishchandra, M.N. Subhash, S. Rao, D. Subbakrishna, Early onset Parkinson's disease: are juvenile- and young-onset different? Mov. Disord. 9 (5) (1994) 539–544.
[68] N. Niemann, J. Jankovic, Juvenile parkinsonism: differential diagnosis, genetics, and treatment, Parkinsonism Relat Disord 67 (2019) 74–89.
[69] L. Vela-Desojo, D. Urso, M. Osuna-Lopez, J. Hoenicka, Non-motor symptoms in pla2g6-associated dystonia-parkinsonism: a case report and literature review, J. Clin. Med. 11 (6) (2022).
[70] M.M. Wickremaratchi, Y. Ben-Shlomo, H.R. Morris, The effect of onset age on the clinical features of Parkinson's disease, Eur. J. Neurol. 16 (4) (2009) 450–456.
[71] M.D. Knipe, M.M. Wickremaratchi, E. Wyatt-Haines, H.R. Morris, Y. Ben-Shlomo, Quality of life in young- compared with late-onset Parkinson's disease, Mov. Disord. 26 (11) (2011) 2011–2018.
[72] A. Sauerbier, K.R. Chaudhuri, Non motor symptoms in Parkinson's disease. , 6 ed., Wolters Kluwer2015.
[73] K. Ray Chaudhuri, V. Leta, K. Bannister, D.J. Brooks, P. Svenningsson, The noradrenergic subtype of Parkinson disease: from animal models to clinical practice, Nat. Rev. Neurol. 19 (6) (2023) 333–345.
[74] P. Tall, M.A. Qamar, L. Batzu, V. Leta, C. Falup-Pecurariu, K. Ray Chaudhuri, Non-oral continuous drug delivery based therapies and sleep dysfunction in Parkinson's disease, J. Neural. Transm. 130 (11) (2023) 1443–1449.
[75] V. Metta, H. Ibrahim, T. Loney, H.T.S. Benamer, A. Alhawai, D. Almuhairi, A. Al Shamsi, S. Mohan, K. Rodriguez, J. Mohan, M. O'Sullivan, N. Muralidharan, S. Al Mazrooei, K. Dar Mousa, G. Chung-Faye, R. Mrudula, C. Falup-Pecurariu, C. Rodriguez Bilazquez, M. Matar, R. Borgohain, K.R. Chaudhuri, First two-year observational exploratory real life clinical phenotyping, and societal impact study of Parkinson's disease in Emiratis and expatriate population of United Arab Emirates 2019-2021: the EmPark study, J Pers Med 12 (8) (2022).

[76] T. Schirinzi, P. Grillo, G. Di Lazzaro, H. Zenuni, C. Salimei, K. Dams-O'Connor, G. M. Sancesario, N.B. Mercuri, A. Pisani, Effects of head trauma and sport participation in young-onset Parkinson's disease, J. Neural. Transm. 128 (8) (2021) 1185–1193.

[77] F. Colucci, M. Avenali, R. De Micco, M. Fusar Poli, S. Cerri, M. Stanziano, A. Bacila, G. Cuconato, V. Franco, D. Franciotta, C. Ghezzi, M. Gastaldi, A.E. Elia, L. Romito, G. Devigili, V. Leta, B. Garavaglia, N. Golfre Andreasi, F. Cazzaniga, C. Reale, C. Galandra, G. Germani, P. Mitrotti, G. Ongari, I. Palmieri, M. Picascia, A. Pichiecchio, M. Verri, F. Esposito, M. Cirillo, F. Di Nardo, S. Aloisio, M. Siciliano, S. Prioni, P. Amami, S. Piacentini, M.G. Bruzzone, M. Grisoli, F. Moda, R. Eleopra, A. Tessitore, E.M. Valente, R. Cilia, Ambroxol as a disease-modifying treatment to reduce the risk of cognitive impairment in GBA1-associated Parkinson's disease: a multicentre, randomised, double-blind, placebo-controlled, phase II trial. The AMBITIOUS study protocol, BMJ Neurol Open 5 (2) (2023) e000535.

[78] A.M. Podlewska, L. Batzu, T. Soukup, N. Sevdalis, I. Bakolis, F. Derbyshire-Fox, A. Hartley, A. Healey, A. Woods, N. Crane, C. Pariante, K. Ray Chaudhuri, The PD-Ballet study: study protocol for a randomised controlled single-blind hybrid type 2 clinical trial evaluating the effects of ballet dancing on motor and non-motor symptoms in Parkinson's disease, BMC Complement Med Ther 24 (1) (2024) 41.

[79] C. Simonetta, J. Bissacco, M. Conti, R. Bovenzi, C. Salimei, R. Cerroni, M. Pierantozzi, A. Stefani, N.B. Mercuri, T. Schirinzi, Motor cortex transcranial direct current stimulation improves non-motor symptoms in early-onset Parkinson's disease: a pilot study, J. Neural. Transm. 131 (2) (2024) 189–193.