



Lifespan Development: Symptoms Experienced by Individuals with Neurofibromatosis Type 1 Associated Plexiform Neurofibromas from Childhood into Adulthood

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Abstract

This secondary data analysis qualitatively identified salient concerns reported by individuals with Neurofibromatosis Type 1 (NF1)-associated plexiform neurofibromas (pNFs) at different stages of development. Past literature has focused on overall symptomatology, but has not examined nuances in how these symptoms are experienced across developmental phases. Therefore, we aimed to identify commonalities and differences in symptom experiences across age groups to better assist individuals to adjust to symptoms across the lifespan. Thirty-one children, adolescents, and adults (age ≥ 5 years old) and 15 parents participated in semi-structured interviews. Analyses focused on the following symptom categories: pain, social functioning, physical function impact, and stigma. Aspects of pain endorsed by all age groups included localized brief pain on contact with pNF and abnormal sensations; however, only adolescents and adults reported chronic pain and change in pain over time. Social functioning themes of limited activity participation, role limitations, and relationship impact were endorsed by all age groups, but differences emerged across age groups in the types of activity and role limitations, the type of relationship impact, and family planning concerns. All age groups described difficulty with mobility, but only parents reported problems with coordination and physical developmental milestones. While all age groups reported external stigma, internalized stigma was predominately endorsed by adults. While individuals in all age groups described pNF concerns related to pain, social function, physical function, and stigma, specific aspects of these symptoms differed across the developmental continuum. These findings can help assist individuals with pNF better transition to the next developmental phases.

Keywords Neurofibromatosis Type 1 · Plexiform neurofibroma · Qualitative · Symptoms · Lifespan

Introduction

Neurofibromatosis Type 1 (NF1) is a common autosomal dominant disorder involving the development of nerve sheath tumors that affects 1 in every 2700 people (Evans et al., 2010). Nerve sheath tumors are abnormal growth of cells in the layer that insulates the nerve fibers that connect the body to the brain. Symptoms of NF1 include brown spots on the skin (café au lait spots), freckles in the groin and armpit, bumps under the skin (neurofibromas), bone abnormalities, and cognitive effects. Among those with NF1, 25–50% develop plexiform neurofibromas (pNFs) (Korf, 1999; Mautner et al., 2008), benign tumors of the peripheral nerves that confer substantial morbidity including organ dysfunction, disfigurement, and malignant potential. Although pNFs generally grow fastest in the first several years of life (Dombi et al., 2007), tumor growth rates vary across individuals and through the lifespan, rendering pNFs

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chronic and unpredictable (Tucker et al., 2009). Thus, individuals with pNFs require lifelong specialized care and support (Van Lierde et al., 2013).

Transitioning across the developmental phases can be further complicated by a chronic medical condition, such as pNF (Kirk, 2008). The current literature primarily focuses on the transition of young adults with NF1 as they increasingly assume greater responsibility for their medical care (Tucker et al., 2009), but there is limited research on the psychosocial and physical impacts of pNF across the lifespan. Various factors may influence an individual's transition across developmental stages such as tumor size, location, malignant transformation, and the organ systems/body region involved. Considerable evidence supports the impact of NF1 on the daily lives of children and adolescents (Graf, Landolt, Mori, & Boltshauser, 2006), particularly during adolescence given that appearance concerns become more salient (Barke, Coad, & Harcourt, 2016). In adulthood, reported social effects include reduced social networks, difficulties in forming relationships, lower educational achievement, and higher unemployment rates (Hummelvoll & Antonsen, 2013). Although past research has examined the impact of NF1 as overall symptomatology (e.g., physical domain, social domain, emotional domain) in different age groups, to-date, research has not investigated differences in these symptom domains across different age groups in a qualitative manner. A better understanding of common and unique experiences within each symptom domain across age groups would provide information to enable clinicians to better assist individuals with pNF manage their symptoms as they transition across developmental stages.

Our previous work utilizing qualitative symptom concept elicitation interviews in a sample of children, adolescents, and adults with pNF (Lai, Jensen, Patel, Listernick, & Charrow, 2017) found that individuals with pNFs across age groups (children, adolescents, and adults), parents, and clinicians identified similar domains of concerns impacting individuals' quality of life. Accordingly, we established a conceptual framework across the lifespan to enable patient-reported outcome measurement of children's and adult's symptoms and health-related quality of life longitudinally using a methodologically rigorous manner that incorporates the "patient perspective" in the development of the measure battery. Despite this commonality in domains of concern, the impact of symptoms may be shaped by individuals' life experiences which differ across different stages of the lifespan. Thus, it is important to understand individuals' concerns beyond overall symptomatology and to examine how aspects of these symptoms may be experienced differently at different points of individuals' lives. Therefore, in this study we took a further step to investigate the similarity and diversity of symptom experiences within the domains of pain, social functioning, physical functioning, stigma among

children, adolescents, and adults with pNFs across the lifespan. We anticipate this understanding can help clinicians plan appropriate interventions to help individuals transition to the next developmental phases and help children with pNFs and their families understand what to expect upcoming challenges at the next phases of their developmental spectrum.

Methods

This study was exempted from review by the Northwestern University Institutional Review Board and was approved by the Institutional Review Board of the Ann & Robert H. Lurie Children's Hospital of Chicago.

Participants and Procedures

This secondary data analysis examined data obtained from a previously published study (Lai et al., 2017). Participants included children and adults with pNFs age 5 years and older and parents of children age 5–17. Participants with a diagnosis of pNF, who were fluent in English, and able to participate in a verbal interview were identified via referrals from the NF1 Clinic at the Ann & Robert H. Lurie Children's Hospital of Chicago and the Children's Tumor Foundation NF Patient Registry. Five children with pNFs per age group (5–7, 8–12, 13–17) and 16 adults with pNFs (18 years and older) were recruited to capture concerns across the lifespan.

Individual telephone interviews (30–60 min in length) were conducted by a trained researcher (SJ or ZP), using an age-appropriate semi-structured interview guide. All parent interviews were conducted prior to their children's interviews to assess the children's understanding of their condition and to respect family communication about pNF. To minimize bias, the same interviewer did not interview the same child–parent dyad when possible. The interviews included a series of open-ended questions about the way in which the participants' lives had been affected by pNFs and the impact of pNF symptoms on different aspects of their quality of life. Open-ended questions were followed by probes to collect additional details when appropriate. All interviews were audio recorded and transcribed by a professional medical transcription service.

Data Analysis

The research team employed selective qualitative analysis methods and an iterative coding process to identify common themes, create codebook definitions, and develop coding rules to apply to interviewees' comments using methodology previously described (Lai et al., 2017). In the initial study, the transcripts were reviewed by trained researchers

to develop a codebook that was then used to code major symptom themes and sub-themes. Transcripts were coded by two independent researchers, with a subset of transcripts coded in duplicate to allow for comparison. Discrepancies in coding were resolved by discussion and consensus between the two coders. Coding was conducted using the “comment” function in Microsoft Word. For the current study, we reviewed the coded data to qualitatively compare participant experiences across age groups and identify the most salient concerns at different time points across the lifespan.

Results

Participant Characteristics

Thirty-one children and adults with pNFs (5–7 years old $n=5$, 8–12 years old $n=5$, 13–17 years old $n=5$, 18 years and older $n=16$) and 15 parents participated in individual interviews across groups, participants ranged in age from 5 to 72 years. Overall, participants were 54.8% female, and 51.6% White. The self-reported (participants aged 8 years or older) or proxy-reported (parents of participants aged 5–7 years) number of pNFs per participant ranged from one to four, with a mean of 1.3. The location of the pNFs varied considerably across participants, with the head area and legs constituting the most common locations across groups. Children and adult participants’ time since diagnosis ranged from 3 to 70.5 years, with a mean of 18.45 years since diagnosis. Parents were predominantly female (80%). Additional

sociodemographic and clinical characteristics for each age group have been previously reported (Lai et al., 2017).

Major Concerns Associated with NF1 and pNF

Across the domains of pain, social function, physical function, and stigma, a subset of themes emerged as commonly endorsed regardless of age group, whereas another subset of themes varied across age groups (See Fig. 1). The commonality and diversity of symptom themes are discussed below, with illustrative participant quotations displayed in Tables 1 and 2. For the purpose of qualitative analysis, the “children with pNFs” group included participants 5–12 years old, the “adolescents with pNFs” group included participants 13–17 years old, and the “adults with pNFs group” included participants 18 years of age and older.

Pain/Sensation

Across the child, adolescent, adult, and parent groups, pain descriptions did not differ considerably, suggesting stability in the pain experience during different points in the developmental continuum. Forty-one percent of participants across all age groups described acute episodes of localized pain in proximity to the site of the pNF. Most participants described this pain as resulting from contact with or pressure applied to the pNF site. Participants in all age groups reported this type of pain as typically resolving in several seconds to several minutes without intervention. Individuals with pNFs across all age groups described their perceived need to be

Diversity in Themes across Age Groups

Commonality in Themes across Age Groups

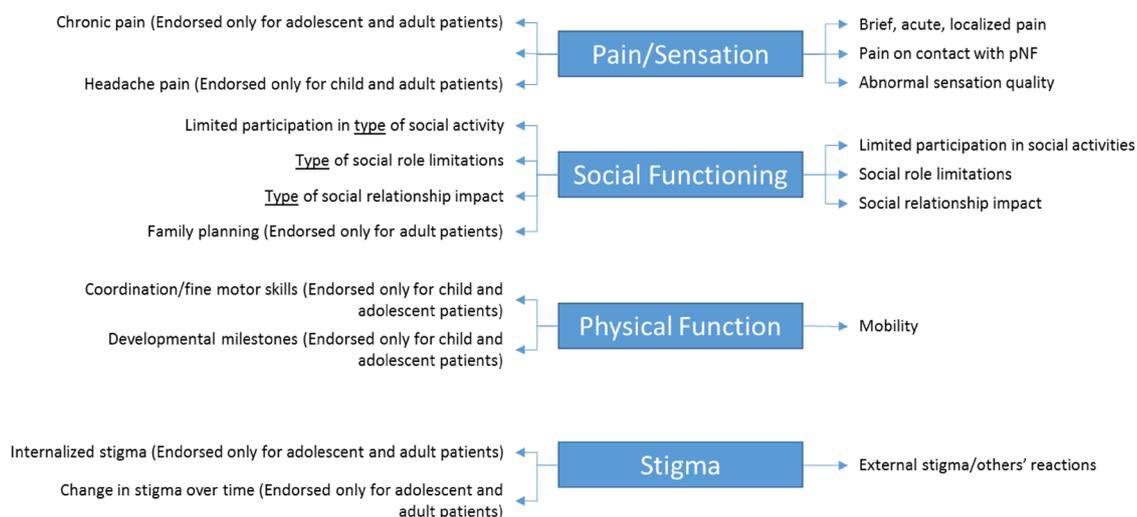


Fig. 1 Diversity and commonality of themes across age groups

Table 1 Participant quotations illustrating commonality in themes across age groups

Domain	Sub-domain	Children 5–7 years old	Adolescents 13–17 years old	Adults 18 years and older
Pain	Acute, pain on contact with pNF	“It seems like it is very temporary it doesn't seem like it goes on, it is in that moment, by pressing on them I guess is when it hurts but beyond that it is doesn't seem like it lingers.” (Participant #014p, parent of 5–7-year-old patient)	“...The other pain is like when you touch it it's more of like kind of a pressure pain, like a pain if you get a bruise and then you push on it.” (Participant #007c, 13–17-year-old patient)	“There was no chronic or persistent ongoing pain. It would just be if somebody would accidentally bump into it or if I accidentally bumped into a desk or something like that or just contact.” (Participant 011a, adult patient)
	Abnormal sensation	“Sometimes they [tumors] tickle.” (Participant #014c, 5–7-year-old patient)	“...And she'll have like pain going and numbness in her hand almost, she's like it's when your foot falls asleep and then it starts to wake up that tingling feeling...” (Participant #007p, Parent of 13–17-year-old patient)	“...Like if you hit your elbow it kind of tingles and the tingling would last for a little longer and be a little more intensified...” (Participant #012a, adult patient)
Social functioning	Participation in activities	“He can't always keep up with physical activities, so if they are playing a game that is more physical he is the slowest one on those things.” (Participant #017p, Parent of 5–7-year-old patient)	“I guess it's not being able to do as many activities as other kids might be able to do.” (Participant #004c, 13–17-year-old patient)	“I always feel like the party pooper because when I go out and have fun, my body starts to hurt from all the walking and I need to sit down or go back home and lie down.” (Participant #007a, adult patient)
	Role limitations	“Well actually this year has been a bit of a change for her—she is in first grade and she actually has an IEP now in school that is specifically targeted with the vision and some of her physical needs.” (Participant #013p, parent of 5–7-year-old patient)	“Well, I always miss a lot of school sometimes.” (Participant #005c, 13–17-year-old patient)	“It does take a lot of time and effort and it's time consuming and doctors appointments are...like I might have to miss work for that. So yeah, I always kind of have that in mind and it's a pretty balancing act.” (Participant #003a, adult patient)
Physical function	Relationship impact	“Yes there have been a couple of kids who are not very nice children and will say I don't want to play with her she looks scary...” (Participant #013p, Parent of 5–7-year-old patient)	“There are socialization issues related to his NF that prevented him from being a very outgoing kind of, he's friendly and he'll talk to people one on one, but he's not real outgoing in terms of, you know, inviting kids over or getting invited to other kid's parties... he doesn't take that extra step to connect with people” (Participant #002p, Parent of 13–17-year-old patient)	“...Actually I actually have never been in a relationship. That's one of the reasons I always felt like an outcast and no one would be accepting of my problem or my condition...” (Participant #011a, adult patient)
	Mobility	“...The walking, the tempo is weird...” (Participant #006p, Parent of 8–12-year-old patient)	“He can't stay on his feet for long periods of time because of the swelling that occurs, so we do get, if we go to an amusement park or something, a disability pass” (Participant #002p, Parent of 13–17-year-old patient)	“And that affects my mobility, that's about all but nothing that I can't handle...you just slow down and it's harder to get around and do the things you were doing...” (Participant #005a, adult patient)

Table 1 (continued)

Domain	Sub-domain	Children 5–7 years old	Adolescents 13–17 years old	Adults 18 years and older
Stigma	External stigma	“Well, some friends they notice stuff so they asked like what’s this particular spot and I don’t really want to like explain all of the things so I just say it’s like a birthmark, but I don’t know . . .” (Participant #008c, 8–12-year-old patient)	“...There’s like a little kid around our neighborhood that likes to call her names...” (Participant #007p, Parent of 13–17-year-old patient)	“...And sometimes people, usually children, they’re curious. They might give you a little bit of a stare and so that’s, for me, always made aware of that, that I have this different thing” (Participant #003a, adult patient)

careful during and/or limit their participation in physical activities as a result of this experience.

Although not identified as a concern among children or their parents, a subset of adolescents and adults described their pain experience as more chronic in nature. Across the adult and adolescent age groups, while some participants reported experiencing “constant” pain, others described experiencing episodic pain consistently over time. Participants who endorsed chronic pain as a concern described it as more debilitating than the acute localized pain, resulting in mobility difficulties and the need for pain management interventions. Participants who endorsed more chronic pain attributed this to various sources, including prolonged periods of activity, sitting or standing in certain positions, and to the pNF itself.

Adolescent and adult participants were uniquely able to report on their perception of how their pain experience has changed over time since their childhood. A subset of adults with pNFs described worsening of their pain over time. One adolescent participant reported worsened pain during adolescence compared with childhood, and one adult described an increase in her pain during puberty, though noting that pain has had less of an impact now that she is an adult.

A subset of children, adolescents, and adults with pNFs and parents endorsed headache pain. Although several participants described chronic or severe headache, the majority reported experiencing occasional, brief headaches. While one adult with pNF expressed her perception that her headache has worsened over time, several parents noted that their children’s headaches have either improved or become less bothersome over time.

Although experiencing abnormal sensations was reported primarily by adult participants, a subset of children, adolescents, and parents also endorsed this symptom. Across age groups, the majority described a tickling or tingling sensation or numbness at the site of their pNF. Other participants reported experiencing burning or “squishy” sensations related to their pNF. No participants described a change in abnormal sensations over time nor substantial impact from this symptom.

Social Functioning

The overall impact of pNF on social roles and activities emerged as a common theme across all age groups. However, different aspects of social functioning appeared more salient among certain age groups, suggesting that the way in which pNF affects social functioning contexts may change during the developmental continuum.

Participants across all age groups described the impact of pNF on their ability to participate in leisure activities. Children and adolescents described limited ability to participate in athletic activities, organized sports, or physical

Table 2 Participant quotations illustrating diversity in themes across age groups

Domain	Sub-domain	Children 5–12 years old	Adolescents 13–17 years old	Adults 18 years and older
Pain	Chronic pain	Not endorsed as a relevant theme	<p>“Some of them hurt, well, the ones that hurt all the time I got removed.” (Participant #008c, 13–17-year-old patient)</p> <p>“...Through puberty I guess the appropriate term was a real ‘pain in the butt’ so to speak because my body was growing and unfortunately the fibroma wasn’t keeping up with the growth of my body so the slightest touch would cause excruciating pain...But once I became, once I stopped growing and the sensitivity went away...” (Participant #011a, adult patient)</p> <p>Not endorsed as a relevant theme</p>	<p>“Because there are some days where I’ve had it hurt so bad that I have to take off from work...Even though there is pain medications sometimes that help out, I still have bad days.” (Participant #006a, adult patient)</p> <p>“...So as an adolescent, pre-teen, I always had to be very careful about not bumping into anything otherwise the pain would send me through the roof, but as an adult, it really hasn’t impacted my life that much.” (Participant #011a, adult patient)</p>
	Change over time	Not endorsed as a relevant theme	<p>“...When he was younger, but they were sudden onset and they were pretty intense, but they were brief, so we never needed medication for them or anything and he had some double vision, but this all occurred when he was much younger and they, they went away on their own...” (Participant #002p, parent of 13–17-year-old patient)</p>	<p>“It feels but it’s not what you would call a normal headache. There’s a lot of pressure. It feels a lot like pressure, almost as if someone has my head in a vice grip and it’s just tightening it down.” (Participant #013a, adult patient)</p>
Social Functioning	Limitation—physical versus non-physical	<p>“I think so the boys his age really are all doing sports and involved in athletic endeavors and he really isn’t.” (Participant #014p, Parent of 5–7-year-old patient)</p>	<p>“I would like to do physical activities, I would like to play sports and I would like to be more in gymnastics but because of the disease I can’t do any of that.” (Participant #007c, 13–17-year-old patient)</p>	<p>“I always feel like the party pooper because when I go out and have fun, my body starts to hurt from all the walking and I need to sit down or go back home and lie down.” (Participant #007a, adult patient)</p>
	Limitation—school versus work	<p>“He does get physical and occupational therapy at school, which at the moment he is okay with, although sometimes it bothers him that he has to leave class to go and do those things because he would rather just be in class with his buddies.” (Participant #017p, parent of 5–7-year-old patient)</p>	<p>“...It makes me sad sometimes too because I want to be either an emergency room nurse and emergency medicine nurse or be an EMS and both of those require lots of physical activity...” (Participant #007c, 13–17 years old)</p>	<p>“Because there are some days where I’ve had it hurt so bad that I have to take off from work and literally just [sit] on the couch and relax...” (Participant #006a, adult patient)</p>

Table 2 (continued)

Domain	Sub-domain	Children 5–12 years old	Adolescents 13–17 years old	Adults 18 years and older
	Relationship difficulty—peer versus romantic	“He doesn’t feel comfortable sometimes playing with children his own age. He feels more comfortable playing with kids maybe 2 years younger than him.” (Participant #011p, parent of 8–12-year-old patient)	“...He has little buddies in our neighborhood that are 3 and 4 years younger than he is that he hangs out with but he does not really socialize with kids his own age just because he’s, you know, different.” (Participant #004p, parent of 13–17-year-old patient)	“Yeah, it changes you socially because you don’t, it’s hard for people that love you to see you in pain or to see you struggle with this and I’ve had people, unfortunately, I lost a marriage throughout this whole deal of being sick and it was just too much. It was too much on the relationship, it was too much.” (Participant #013a, adult patient)
	Family planning	Not endorsed as a relevant theme	Not endorsed as a relevant theme	“I’d probably say if I were in a relationship the fact that I am not willing to have kids, I know that’s a big downer for some people, because I don’t want them to have NF....” (Participant #011a, adult patient)
Physical Function	Coordination/fine motor skills	“...He is very uncoordinated, and his fine motor skills are not great so his handwriting is pretty bad...” (Participant #014p, Parent of 5–7-year-old patient)	“He’s not very coordinated so, you know, that’s I think is because of the NF so even though he likes to play I don’t think and I guess you could say that might have impacted his life a little bit.” (Participant #005p, Parent of 13–17-year-old patient)	Not endorsed as a relevant theme
	Developmental milestones	“...He can’t always keep up with friends. He can’t do those fully monkey bars and most of the kids can do the monkey bars. He can’t run as fast. He can’t jump as high as the kindergarten and first grade boys who are very physical....” (Participant #017p, Parent of 5–7-year-old patient)	“...Because of his vision and his coordination issues and, well, he’s always been developmentally delayed kind of a couple years behind his peers just socially and physically so he is doesn’t seem to be physically to the point of driving yet and he’s 16.” (Participant #004p, parent of 13–17-year-old patient)	Not endorsed as a relevant theme
Stigma	Internalized stigma	Not endorsed as a relevant theme	“...I guess I didn’t really start becoming more aware of it until middle school when getting changed in gym class and all that stuff. I became more aware of everything going on with my body...I just always felt embarrassed and not pretty and all that stuff.” (Participant #016a, adult patient)	“To me, it’s like a big eye sore...that is more psychologically bothersome, you know, because it is the one that I cannot hide... So I think that’s the biggest obstacle for me physically, mentally is the cosmetic part of it.” (Participant #014a, adult patient)

Table 2 (continued)

Domain	Children 5–12 years old	Adolescents 13–17 years old	Adults 18 years and older
Sub-domain	Children 5–12 years old	Adolescents 13–17 years old	Adults 18 years and older
Change over time	Not endorsed as a relevant theme	“I had to, you know, get changed in the bathroom stall because I didn’t want to get changed in front of my friends.” (Participant #016a, adult patient) [referring to gym class as an adolescent]	“...Then as I got older, I just became more self-conscious of it. So, you know you do things to hide it.” (Participant #014a, adult patient)

play due to their different athletic abilities in comparison to peers, to intentional avoidance (at times per the parents’ decision), and to being physically unable to participate. Children, adolescents, and parents all cited pain, tumor location, and impact on physical function as the reasons diminished opportunities for social interaction. Several children, adolescents, and adults also described a limited ability to participate in non-physical social activities, such as hobbies, community activities, and social activities with friends.

Children, adolescents, and parents reported that pNF affected their participation in school. Participants described missing school frequently due to medical appointments and pain. A subset also spoke about needing modifications to participate in different aspects of school, such as special positioning/seating in the classroom and modified participation in physical education class. Similarly, adults reported that frequent medical appointments and pain also resulted in missed work. Several adolescent and adult participants spoke about the impact of pNF on their vocational decision-making and described feeling discouraged by the possibility of being unable to pursue their desired professions.

In addition to the ability to participate in social activities and roles, a subset of adults expressed diminished interest in participating in social activities as a result of their discomfort in social situations due to pNF. Although not endorsed directly by children or adolescents, several parents reported observing voluntary avoidance of social activities, explaining that their children prefer solitary activities to socializing outside of the home. They also expressed their belief that their children appear content to not engage in social activities.

Difficulty forming and maintaining social relationships also emerged as an aspect of social functioning with some differences across age groups. A subset of adults noted difficulty forming romantic relationships despite a desire to do so, and several specifically attributed this to pNF. While children and adolescents did not describe difficulties with social relationships, this was a common theme reported by their parents, who often spoke of bullying due to differences in appearance and social skills compared to peers. Several parents noted that their children tend to form social relationships with children younger than them, or those with similar cognitive or social skills limitations.

The impact of pNF on family planning represented a concern unique to adults with pNFs, who reported concerns about having a biological child due to the genetic nature of pNF, as well as the potential effect of hormonal changes during pregnancy on their pNF symptoms. Several discussed the potential impact of family planning on their current and future romantic relationships.

Physical Function Impact

The impact of pNF on physical function emerged as more salient during the childhood and adolescent years, although some aspects of physical function impact were still noted by adults. Despite being cited as a specific concern among parents of children and adolescents, impact on specific aspects of physical function was rarely noted by children and adolescents themselves, which may reflect their tendency to focus on the outcome of physical function impact, such as activity limitations (described above).

Parents described coordination as an area commonly affected by pNF, reporting difficulties with general coordination and fine motor skills. Difficulty with handwriting was frequently cited as an example of physical function impact by parents, as well as a subset of adult participants.

Both parents and adults also identified mobility as an aspect of physical function impacted by pNF. Parents described mobility impact in terms of overall ability to walk, gait speed, and endurance, with several noting the occasional need for assistive devices (e.g., wheelchair) or services (e.g., disability pass at amusement park). Parents expressed their perception that their children's mobility problems resulted from multiple factors, including muscle tone, swelling, and difficulty with balance and spatial perception. A subset of adults also reported mobility impact related to ability to walk and gait abnormalities.

Parents also discussed physical function impact in the context of delays in achieving developmental milestones in comparison to peers such as learning to walk, running ability, jumping ability, ability to ride a bike, and ability to effectively use playground equipment.

Stigma

Stigma associated with having pNF represented a psychosocial concern identified primarily by adults with pNFs and parents. Child and adolescent participants described stigma notably differently than adults. Specifically, stigma experienced during childhood and adolescence was characterized by greater emphasis on others' awareness of and response to the pNF (external stigma), whereas stigma experienced during adulthood was characterized by a more internalized emotional body image response to the pNF (internal stigma).

Adults with pNFs and parents commonly described stigma in the context of other people's behavior toward them highlighted others' awareness of their pNF or of being "different." Participants of all age groups identified receiving questions from others about their pNF as a common source of stigma. Although most acknowledged that such questions likely stemmed from others' curiosity, they expressed that it was bothersome to have to explain their condition to peers

and strangers. Adults with pNFs and parents also cited others staring at the pNF as part of the stigma they experience.

A subset of parents expressed concern about their children possibly experiencing a more overt stigma experience characterized by teasing and bullying. The experience of being teased during childhood/adolescence because of their pNF was also endorsed by a subset of adults with pNFs.

Adult participants' emphasis of internalized stigma related to body image represented a notable difference from other age groups. Many adults reported feeling "self-conscious" due to the appearance of their pNF. Several described this in the context of visible exposure of the pNF, such as when wearing certain attire, when changing clothes, or when the location of the pNF was always visible. Several adults reported efforts to conceal their pNF. A subset acknowledged that the appearance of their pNF may be less notable to others than it is to the them personally.

A number of children and adults with pNFs and parents spoke directly about perceived changes in stigma over time. Several parents of children expressed their perceptions that with age, other children seemed to "notice" the pNF more, resulting in questions and staring. One mother cited an increase in her child being bothered by others' reactions to her pNF since beginning school. One adolescent reported that she had experienced more teasing about her pNF when she was "really younger" and several adults noted experiencing the most teasing during childhood. A subset of adult participants retrospectively identified adolescence as a time when stigma emerged as a prominent concern. Adult with pNFs varied in their description of how their stigma experience has changed as an adult, with some citing improvements and others describing persisting difficulties.

Discussion

Managing the challenges from developmental transitions is complicated in and of itself, and it is even more challenging for individuals who need to deal with the symptoms from a non-curable condition. In this study, we cross-sectionally assessed pNF impacts on pain, social function, physical function, and stigma across developmental stages, with an ultimate goal of enhancing interventions to help patients and families to better prepare for potential challenges. These symptom categories were chosen because they were identified as common concerns for individuals with pNF in our previous study (Lai et al., 2017). Findings suggest that each of these symptom categories is relevant across all age groups with certain aspects being more salient at different developmental phases.

Participants described their pain experience fairly similarly across age groups, suggesting consistency in pain experiences. Individuals with pNFs commonly reported

experiencing episodes of acute, localized pain that was typically brief and in response to physical contact with the tumors; yet some adolescents and adults described a more chronic pain experience and perceived worsening of pain over time. This is consistent with previous findings that NF1 manifestations increase with age (Friedman, 2002), and greater pain reported by adults 26–37 years old than 18–25 years olds (Hummelvoll & Antonsen, 2013). Parents of children and adolescents with pNFs may need to be educated about the potential worsening of their child's pain over time and be provided with appropriate pain management skills.

Previous research suggests that increased age predicts significant worsening in social functioning (Merker et al., 2014). In this study, reports of pNF impacts on social function qualitatively differed across age groups, likely reflecting differences in social opportunities. Participants of all age groups described a limited ability to participate and intentional avoidance of social activities, resulting in fewer opportunities for social interaction. Potential deficits in prosocial behavior among adults with NF1, as indicated by literature (Pride, Crawford, Payne, & North, 2013) and confirmed by our work, suggest that children and adolescents with pNF may benefit from social skills training (Martin et al., 2012). Consistent with the literature (Crawford et al., 2015; Hummelvoll & Antonsen, 2013), adults and parents expressed difficulties in the formation and maintenance of social relationships. For instance, Hummelvoll and Antonsen found adults with NF1 had more friends in childhood compared to young adulthood and that maintaining friendships was very important to 18–25 year olds (Hummelvoll & Antonsen, 2013). In our sample, adults placed greater emphasis on pNFs adversely affecting romantic relationships and family planning. Similarly, Crawford et al. reported participants attributed the inability to find partners and the lack of social intimacy due to the anticipated rejection from the disclosure of their diagnosis (Crawford et al., 2015).

Participants of all age groups noted impacts of pNF on their social roles, although this appears to be associated with developmental differences in relevant social roles. Parents described their children's experience with social relationships in the context of bullying and their children's preference for relationships with peers who were younger and/or had similar cognitive developmental limitations. Children and adolescents described the impact of pNF and its associated treatment on their school experience, whereas adults described the impact on work and vocational decision-making. This is consistent with previous findings indicating that adults with NF1 associate their perception of their experience with impacts on social networks and employment, rather than solely disease severity (Hummelvoll & Antonsen, 2013).

In contrast to previously reported associations between increased age and decreased physical function in NF1 (Merker et al., 2014), we found physical function impact represented a more prominent concern for children and adolescents with pNF. Consistent with previous findings suggesting that children and adolescents with NF1 develop negative self-concepts related to physical abilities (Barton & North, 2007), in this study children often related physical function to social participation by describing the effects of physical function in terms of activity limitations. Parents emphasized impacts on developmental milestones and skills that might affect instrumental activities of daily living. However, the infrequent report of physical function impact among adults may be due to their adaption to such limitations since their childhood.

Although participants in all age groups experienced stigma, it was noted most by adults and parents. Similar to previous literature (Barke, Harcourt, & Coad, 2014), retrospective adult reports characterized childhood stigma experiences as mostly external, such as others asking questions, staring, and teasing them. Parent reports also indicated a perceived increase in stigma over time as other children developed greater awareness of their child being “different.” Although adults and adolescents noted that external aspects of stigma persisted with age, they developed a more internalized stigma related to body image. Many described the emergence of feeling “self-conscious” because of pNF during adolescence, which coincided with previous findings (Crawford et al., 2015) that perceived stigma related to cosmetic signs of NF1 was bothersome to participants across all degrees of visibility and disease severity (Crawford et al., 2015).

Study Limitations

This study aimed to examine the symptoms experienced by individuals with pNFs at different developmental stages to assist families to better prepare for the developmental transitions by identifying possible challenges and providing appropriate interventions. Given the nature of a secondary data analyses, several limitations were noted. First, our conclusions derive from cross-sectional data, and whether the results can be generalized to the trajectory of patients' experiences need to be further evaluated. The differences between age cohorts might reflect generational cohort effects, such as changes in sociocultural perception of chronic illness or visible disfigurement over time. Therefore, studies should be conducted to monitor individuals with pNFs longitudinally to control for potential cohort effects. Second, our sample size was determined based on the saturation of concerns raised by patients and parents. These interviewees were recruited via a national registry database with an attempt to increase sample diversity; however, we did not employ a

purposive sampling strategy to produce a sample assumed to be representative of the pNF population. Consequently, we cannot state with confidence that the final sample was representative of the pNF population in terms of disease severity (e.g., number, location, or size of pNFs) or sociodemographic characteristics (e.g., race/ethnicity, gender). Acknowledging that symptom burdens and their impacts to patients' well-being are potentially influenced by various factors including disease severity and socioeconomic status, we recommend future research is needed to replicate our findings and to evaluate influential factors to patients' concerns using purposive sampling strategies and a prospective, longitudinal design in a sociodemographically diverse sample across the lifespan. Third, although we sought to identify concerns specific to pNF, we noted some concerns are shared by patients with NF1 without plexiform neurofibromas. It is possible that the participants were unable to differentiate concerns between pNF versus NF1. Consequently, some of the concerns identified may be related more to the overall NF1 experience than the pNF. Finally, interviews with younger children yielded less detailed information than the older age groups, possibly due to their limited communication skills and emerging cognitive abilities. Moreover, it is possible that some children possessed very limited understanding of their disease status as a result of parents' sometimes limited communication with children regarding their condition. We thus relied upon parent reports to supplement the information from the child patient interviews, which may not accurately reflect the children's perceived disease and symptom experiences. As noted by past research, parents report a greater impact of NF1 on the quality of life of their children than their children report (Krab et al., 2009).

Practice Implications

Despite these limitations, this study provides insight into how children and adults with pNFs and their parents perceive pain, social function, physical function, and stigma across age groups. These domains were assessed because they were the most commonly identified by children and adults with pNFs at different developmental phases (Lai et al., 2017). These results may help clinicians better communicate with individuals with pNFs and families about possible challenges they may experience later in their life, and help them prepare for these challenges. This is particularly important as adolescents transition into young adulthood and assume greater responsibility to manage their own condition (Beresford, 2004; Camfield & Camfield, 2011; Kennedy, Sloman, Douglass, & Sawyer, 2007; Van Lierde et al., 2013). Additionally, the findings highlight the importance of assessment of factors such as pain, stigma, social functioning, and physical function given their potential to change over the course of development, as well as changes in their

impact on quality of life over time. Assessment of these domains may provide the opportunity for timely referrals to healthcare professionals, such as mental health providers, pain management, and physical and occupational therapy. The findings also suggest that it may be beneficial to adapt currently existing evidence-based psychosocial interventions to address concepts specific to the experience of pNF across developmental groups, such as including modules specific to coping with pain, stigma, enhancing social functioning and coping with physical function limitations. Future work is needed to explore the adaptation of interventions such as Cognitive Behavioral Stress Management, Mindfulness Based Stress Reduction, Cognitive Behavioral Therapy, Acceptance Based Commitment Therapy, social skills training, and other skills-based interventions (e.g., cognitive disputation, and activity gradation) to address the unique experiences that affect individuals with pNF across the lifespan.

Dissemination of the findings to provide psychoeducational resources to individuals with pNFs and their families represents an important future step. Psychoeducational materials based on these findings should be developed to serve as a valuable resource, not only in the clinical setting, but for NF1 national and regional advocacy and support groups. Future work is needed to explore the best methods of dissemination (e.g., web-based, social media, brochures, and pamphlets) as well as to tailor the information presented to ensure it is developmentally appropriate for different age groups.

Research Recommendations

The findings also have implications for future patient-centered research in NF1 and pNF, including prospective quantitative assessment of these domains across the lifespan, as well as research examining resiliency factors when adjusting to life with NF1-associated pNFs. Additionally, the findings suggest that while the domains themselves are important to compare patients' symptom burden and psychosocial health across age groups as well as to monitor change longitudinally to facilitate timely interventions, the themes within the domains qualitatively differ across age group and, thus, individualized interventions are needed to capture these unique experiences. Patient-centered outcome measures assessing these domains should also take these developmental differences into consideration when assessing patient experience across the lifespan. As noted above, an important future research direction involves the development of age-appropriate psychoeducational materials for use in the pNF clinical and community settings, as well as research to examine the effect of psychosocial interventions adapted to the concerns experienced by individuals with pNFs across the lifespan.

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Compliance with Ethical Standards

Conflict of interest Sally E. Jensen, Zabin S. Patel, Robert Listernick, Joel Charrow, and Jin-Shei Lai declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Participants recruited from the Ann & Robert H. Lurie Children's Hospital of Chicago provided informed consent. Informed consent was not required for all other participants because the study was exempted from review by the Northwestern University Institutional Review Board.

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