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Chronic Pain in Noonan Syndrome: A Previously Unreported but Common Symptom

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Noonan syndrome (NS) is a multiple malformation syndrome characterized by pulmonic stenosis, cardiomyopathy, short stature, lymphatic dysplasia, craniofacial anomalies, cryptorchidism, clotting disorders, and learning disabilities. Eight genes in the RAS/MAPK signaling pathway are implicated in NS. Chronic pain is an uncommon feature. To investigate the prevalence of pain in NS, we distributed a two-part questionnaire about pain among NS individuals at the Third International Meeting on Genetic Syndromes of the Ras/MAPK Pathway. The first part of the questionnaire queried demographic information among all NS participants. The second part was completed by individuals with chronic pain. Questions included musculoskeletal problems and clinical features of pain. Forty-five questionnaires were analyzed; 53% of subjects were female. Mean age was 17 (2–48) years; 47% had a *PTPN11* mutation. Sixty-two percent (28/45) of individuals with NS experienced chronic pain. There was a significant relationship between prevalence of pain and residing in a cold climate ($P = 0.004$). Pain occurred commonly in extremities/joints and head/trunk, but more commonly in extremities/joints ($P = 0.066$). Subjects with hypermobile joints were more likely to have pain ($P = 0.052$). Human growth hormone treatment was not statistically significant among subjects without chronic pain ($P = 0.607$). We conclude that pain is a frequent and under-recognized clinical feature of NS. Chronic pain may be associated with joint hypermobility and aggravated by colder climate. Our study is a preliminary investigation that should raise awareness about pain as a common symptom in children and adults with NS.

Key words: Noonan syndrome; medical genetics; chronic pain; growth hormone; climate; joint hypermobility; Ras-dependent mitogen-activated protein kinase kinase kinase; genotype–phenotype correlations

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INTRODUCTION

Noonan syndrome (NS), first described in 1968 by Jacqueline Noonan, is an autosomal dominant, multiple malformation syndrome [Noonan, 1968]. It is characterized by congenital heart disease in the form of pulmonic stenosis and hypertrophic cardiomyopathy, occasional ventricular septal defect or atrial septal defect, short stature, lymphatic dysplasia with neck webbing, distinct craniofacial features, cryptorchidism, various clotting factor deficiencies, and learning disabilities [Noonan, 2005a; van der Burgt, 2007]. As one of the most common malformation syndromes with an incidence of 1 in 1,000–2,500 births, its phenotype is considerably variable [Sharland et al., 1992]. Eight different genes in the Ras/MAPK signaling pathway have been implicated in NS [Sarkozy et al., 2009; Cirstea et al., 2010; Verloes et al., 2014]. The most common mutations are in *PTPN11*, which cause 50% of cases [Tartaglia et al., 2001].

Chronic pain is not a cardinal feature of NS and medical geneticists do not typically monitor pain during routine genetic evaluations of patients with NS. We surveyed the published reviews of NS, and pain was not listed as a symptom. We identified only three studies, which noted pain as a feature of NS. In a study on 56 adults with NS, Noonan [2005b] reported that subjects frequently endorsed clinical conditions of depression, lymphedema, arthritis, and back pain. Smpokou et al. [2012] described clinical features of NS among a population of 35 adolescents and adults. Chronic joint pain occurred in 54%, chronic back pain in 40%, and chronic muscle pain in 34%. Joint hypermobility and scoliosis each occurred at a frequency of 49%. Reinker et al. [2011] studied orthopedic complications in individuals with Ras/MAPK-related disorders and found that

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chronic pain in all body areas (back, hand, neck/shoulder) occurred more frequently in those with NS (N = 26, $P = 0.001$) than in those with cardiofaciocutaneous syndrome (N = 32) or Costello syndrome (N = 2). Sixty-two percent of NS subjects had scoliosis, serious cervical spine disorders, including cervical stenosis, Arnold–Chiari malformation, or syringomyelia that may have been associated with pain.

Some features of RASopathies are putative causes of chronic pain including autoimmune diseases and Noonan-like/multiple giant cell lesion syndrome (NS/MGCLS). Quaio et al. [2012] reported that among 42 patients ages 4–57 years with RASopathies, 14% had autoimmune diseases and 52% had autoantibodies in their serum. Eight case reports have been published on systemic lupus erythematosus in patients with RASopathies [Bader-Meunier et al., 2013]. The majority of these patients experienced polyarthritis.

NS/MGCLS is a feature of many RASopathies including *PTPN11* and *SOS1* mutations [Jafarov et al., 2005; Wolvius et al., 2006; Beneteau et al., 2009; Neumann et al., 2009]. Multiple giant cell lesions are non-neoplastic granulomas of multinucleated Langhans giant cells embedded in a fibrous stroma. Osteoclast-rich jaw lesions are most common, but there may be no jaw involvement [Beneteau et al., 2009; Bufalino et al., 2010]. These lesions can cause pain.

We report a patient who presented to genetics clinic for the evaluation of chronic pain of unknown etiology; we subsequently diagnosed her with NS. Her pain diminished significantly with human growth hormone (GH) treatment initiated for short stature and slow growth velocity. Following her diagnosis, we became aware of 18 additional self-reported cases of chronic pain in individuals with NS on a NS social media group. These findings prompted us to carry out a survey of pain in NS at the annual RASopathies conference in 2013. Our primary objective was to better understand the nature of the pain and alleviating and aggravating factors. Considering our patient, we were particularly interested in exploring the relationship between climate and pain as well as pain relief with GH therapy in NS individuals.

CASE REPORT

Our patient was a 14-year-old girl referred to genetics clinic for chronic, severe hand and foot pain since the age of 2 years (Fig. 1). Her pain worsened with time and was most severe in the morning. It responded briefly to the application of heat and deep pressure, heated mattress topper, ibuprofen, gabapentin, and acupuncture. She had no erythema, swelling, or Raynaud phenomenon. She was unable to attend school due to unpredictable pain flares and easy fatigability. Pain in her hands made writing difficult. Pain in her knees increasingly limited her ability to exercise. While living in the Midwest, her pain awakened her five to seven nights every week. Her family relocated to the southwest United States (US) from the upper Midwest as her pain was significantly reduced in warmer weather. Following the move, she experienced pain once or twice per week in the winter and less often in the summer.

Our patient's birth weight was eight pounds and six ounces. Birth length was 21 inches. Her past medical history was significant for mitral valve prolapse, hyperopia, chronic abdominal pain due to multiple food allergies, and intermittent dermatitis that coincided with her episodes of pain. She had several past minor fractures, all related to normal childhood trauma, and an Achilles tendon injury from running and dancing. A formal rheumatologic evaluation revealed no evidence of a rheumatologic disorder. There was no family history of NS and no associated clinical features in either parent.

FIG. 1. Photograph of our patient at age 11. Note facial features of Noonan syndrome: borderline macrocephaly, thick coarse, wavy hair; hypertelorism, a wide nasal bridge/tip and full, lax cheeks. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

On physical exam, her height was 135 cm (10–25th centile), weight was 28.9 kg (5–10th centile), and head circumference was 44 cm (98th centile). She had thick coarse hair, hypertelorism with posteriorly angulated ears, a rounded nasal tip; and full, lax cheeks. She had a slight pectus carinatum with widely spaced nipples, velvety skin with several café au lait spots, and scattered erythematous circular lesions. Her joints showed full range of motion without swelling or erythema. She did not have hypermobile joints. Extensive metabolic testing, including DNA for Fabry disease, was negative. Chromosomal microarray revealed a 370 kb microduplication on Xp22.33 and microdeletions of 378 kb on Xq28 and 88 kb on 1 p36.22. Her mother also carried both X chromosome variants. The 1p36.22 microdeletion included only one gene: short-chain dehydrogenase/reductase family member 3 (*DHRS3*). Electromyogram, nerve conduction studies, and spine MRI were negative. MRI of her feet revealed a focal signal abnormality in the distal shaft of the left fourth metatarsal and a small segmental left flexor hallucis longus tenosynovial effusion. She did not undergo evaluation for osteoporosis with DEXA (dual-energy X-ray absorptiometry). Multiple plain films of the thoracic and lumbar spine and hand did not reveal osteopenia, except for a right ankle radiograph that showed evidence of demineralization. A biopsy of her skin rash at the

Mayo Clinic was nondiagnostic. Although, her history of chronic pain was not typical, her physical exam was consistent with NS. This diagnosis was confirmed via DNA testing that revealed the previously reported p.R552S mutation in *SOS1*.

She was evaluated by an endocrinologist for borderline short stature and NS. Insulin-like growth factor 1 was 89 ng/ml (133–416 ng/ml). She started daily treatment with GH injections 0.3 mg/kg/day. Her growth velocity improved appropriately with GH. In the first month of treatment, she experienced a moderate improvement in her pain level. After 2 months of treatment, she had dramatic improvement in her pain symptoms. Her joints, however, have become progressively hypermobile. She is now able to sleep well, and awakens from pain only once every month.

MATERIALS AND METHODS

We designed a two-part questionnaire to collect information about pain among NS individuals. The questionnaire was exempted by the Phoenix Children's Hospital IRB; the research did not involve individual identifiers. The questionnaire was distributed in August 2013 at the Third International Meeting on Genetic Syndromes of the Ras/MAPK Pathway: Towards a Therapeutic Approach. This meeting was concurrent with four family support organizations: Cardio-Facio-Cutaneous Syndrome International, Costello Syndrome Family Network with support from International Costello Syndrome Support Group, Noonan Syndrome Foundation, and Neurofibromatosis Network.

The questionnaire was made available to both adult and child volunteer participants with a self-claimed diagnosis of NS. Subjects remained anonymous and received no compensation. The questionnaire was not introduced or titled as a pain questionnaire to avoid biasing the participants. We included 31 open- and closed-ended questions. The first part of the questionnaire queried demographic information, first three digits of zip code, confirmed genetic mutations, use of GH therapy, and common clinical features of NS (i.e., hypotonia, heart malformations, hair texture, etc.). The second part of the questionnaire was to be completed by individuals who experienced concurrent chronic pain in the last three months. It included questions regarding musculoskeletal problems, prior surgeries, prior fractures, positive findings on imaging, clinical features of pain including alleviating and aggravating factors, Wong–Baker Faces Pain Rating Scale, and evaluation by specialists. We used the Brief Pain Inventory (BPI) to model most questions regarding severity, location on a body map, and pain interference with daily life [Cleeland and Ryan, 1994; Cook et al., 2013; Furler, 2013]. The BPI is a self-report measure and standard assessment of chronic pain and the impact of pain on daily functioning. Patients rate the interference of pain with mood, walking ability, relationships, etc. Each category is rated on a scale of 1–10, where 1 is the least interference and 10 is the greatest interference. Location of pain was inferred from the areas subjects circled on a picture of the human body printed in the questionnaire as modeled by the BPI [Cleeland and Ryan,1994; Furler, 2013]. The two-part questionnaire allowed us to compare the signs and symptoms of NS and demographics of those who experience chronic pain with those who do not. Physical exams were not conducted as part of the survey.

Statistical Methods

Statistical software PASW Statistics 18 (SPSS, Inc., Quarry Bay, Hong Kong) was used for data analysis. Descriptive statistics for all subjects were obtained. Two-sided Fisher exact and Chi-square tests were performed to determine statistical significance of categorical variables including gender, gene mutation, age of onset, pain severity, climate distributions, surgery, location of pain, short stature, GH treatment, and hypermobile joints.

RESULTS

Forty-five questionnaires were submitted at the conference and used in the data analysis. Fifty-three percent of subjects were female. Mean age of subjects was 17 (2–48) years. Forty-seven percent had a *PTPN11* mutation, which is representative of the NS population. Frequencies of genetic mutations, cardiac and neurologic signs and symptoms, locations of pain, and pain interference survey results are presented in Tables I–V. Sixty-two percent (28/45) experienced chronic pain within the last 3 months. We found no significant relationship between gender and pain ($P = 0.233$) or prevalence of gene mutation and pain ($P = 0.595$).

Among pain subjects, 50% (14/28) were <16 years old. Average age of pain onset was 8 (2–14) years (N = 15). Pain and no pain groups had no significant difference in the average age of subjects at time of survey ($P = 0.207$, Table IV). The average severity of pain was 4 ± 1 (N = 24). Among these subjects, we found no significant relationship between age of onset of pain and pain status (i.e., worsening, improving, or unchanged; $P = 0.157$). Eighty-nine percent (24/27) answered that their pain has been either unchanged or worsening.

We compared the number of patients who experience pain in different body parts. Pain was more common in extremities and joints compared to head, neck, trunk, and back ($P = 0.066$; see Table III). Patients with hypermobile joints were more likely to

TABLE I. Gene Mutations of Study Population (N = 45)

Gene mutation	Number of subjects	Frequency in study (%)	Frequency in general NS population
PTPN11	21	47	50%
SOS1	11	24	10–13%
No DNA testing	6	13	NA
KRAS	4	9	<5%
RAF1	1	2	3–17%
SHOC2	1	2	NA
BRAF	1	2	<2%
MAP2K1	0	0	<2%
NRAS	0	0	Four individuals to date
RIT1[a]	NA	NA	3–5%

NS, Noonan syndrome; NA, not available.
[a]*RIT1*, Mutation was published after completion of our data collection.

TABLE II. Cardiac Status: Prevalence in Study Population (N = 45)

Sign/symptom	Number of subjects	Frequency in study (%)
Pulmonary valve stenosis	24	53
HCM	11	24
ASD	11	24
VSD	5	11
Pulmonary artery stenosis	2	4
Coarctation of aorta	2	4
Tetralogy of Fallot	0	0
Pulmonary artery aneurysm	0	0
Other congenital heart defects	8	18
Abnormal EKG	10	22

HCM, hypertrophic cardiomyopathy; ASD, atrial septal defect; VSD, ventricular septal defect.

have pain ($P = 0.052$). Both values approached, but did not reach significance. Headache was prevalent among chronic pain individuals. Forty-eight percent (13/27) had chronic headache. Of these, 15% (2/13) reported Arnold–Chiari malformation. Two other pain individuals had Arnold–Chiari malformation but no chronic headache. We did not confirm this condition with head imaging.

We asked subjects about other symptoms and diagnoses that may relate to pain such as rheumatologic disease, NS/MGCLS, prior surgeries, and osteoporosis. Forty-three percent of chronic pain subjects (12/28) had swelling in the tops of their feet and backs of their hands, and 39% (11/28) had swelling in other areas. Subjects with swelling in hands and feet did not have pain in their extremities ($P = 0.028$). Two subjects with swelling and pain sought care from a rheumatologist. One listed that he/she also experienced periodic fever syndrome, an autoimmune disorder, and joint pain in knees and fingers. Four percent (2/45) had NS/MGCLS and jaw cysts; however, they only experienced pain in their extremities and joints. Eighty-nine percent (25/28) had at least one prior surgery; however, only 21% (6/28) had surgeries related to the location of their pain. There was no significant relationship between a prior surgery related to the site of pain and prevalence of pain ($P = 0.135$). We did not specifically query patients about history of or evaluation for osteoporosis. One patient reported a diagnosis of osteoporosis with DEXA scan and hip fracture. Overall, the prevalence of fractures was low.

Pain interference survey results (Table V) showed that pain affected subjects' daily life regarding general activity, mood, walking ability, normal work, relations with others, and sleep. Patients reported that pain interfered with daily mood at an average of 5 ± 3 ($N = 26$).

We compared the prevalence of pain by climate zone. Forty-four percent (4/9) of subjects from hot climates experienced pain. Eighty-three percent (15/18) of subjects from cold climates experienced pain. Forty percent (18/45) of subjects were from mixed climates, which have both cold and hot weather at different times of the year. Subjects from mixed climates were excluded from climate zone analysis. There was a significant relationship between the prevalence of pain and residing in a cold climate ($P = 0.004$). There was no significant relationship between the prevalence of pain and residing in a hot climate.

Eighty-six percent (24/28) sought medical attention for pain. Sixty-seven percent (16/24) sought care from primary care providers, 46% (11/24) from medical geneticists, 38% (9/24) from physical therapists, 33% (8/24) from orthopedic surgeons, 24% (7/

TABLE III. Location of Pain (N = 28)

Location of pain	Number of subjects[a]
Head and face	7
Trunk: chest, abdomen, and buttocks	7
Neck and back	10
Arm	4
Hand	5
Leg	16
Foot	11
Joints: wrist, knee, and ankle	18

[a]Subjects may have had more than one pain location.

TABLE IV. Comparison of Study Parameters (N = 28)

Study parameters	*P*-value
Gender versus pain	0.233
Any specific gene mutation versus pain	0.595
Age of onset of pain versus pain severity	0.157
Average age of subjects in pain group versus no pain group	0.207
Prior surgery at site of pain versus pain	0.135
Pain in extremities and joints versus pain in head, neck, trunk, and back	0.066
Hypermobile joints versus pain	0.052
Growth hormone therapy versus no pain	0.607
Cold climate versus pain	0.004

TABLE V. Severity of Pain Interference With Daily Life by Category (N = 28)

Pain interference category	Average score[a]
General activity (N = 28)	5 ± 3
Mood (N = 26)	5 ± 3
Walking ability (N = 27)	5 ± 4
Normal work (N = 24)	4 ± 3
Relations with others (N = 26)	3 ± 3
Sleep (N = 27)	6 ± 4

[a]Scale of 1–10, lowest interference of 1 and maximum interference of 10.

TABLE VI. Evaluation of Pain by Specialists (N = 24)

Specialist	Number of subjects[a]	Frequency[a] (%)
Primary care	16	67
Medical genetics	11	46
Physical therapy	9	38
Orthopedic surgery	8	33
Neurology	7	29
Rheumatology	2	8
Psychiatry	2	8
Chiropractor	2	8
Other[b]	8	33

[a]Subjects may have had more than one pain location.
[b]Other includes but is not limited to neurosurgery, physiatry, naturopathy, endocrinology, massage therapy, hypnotherapy, and "all specialties."

24) from neurologists, and 8% (2/24) from a pain clinic (Table VI). Only 8% (2/24) were formally evaluated by a rheumatologist.

We compared GH treatment with prevalence of no pain. Twenty-two percent (10/45) had a short adolescent growth spurt. Fifteen patients received GH therapy at some time, but only five had a "short adolescent growth spurt." GH treatment was not statistically significant among subjects without chronic pain ($P = 0.607$).

DISCUSSION

Chronic pain has not been studied as a cardinal feature of NS, and there is little published information on this topic. The majority of patients in our study (62%) experienced chronic pain.

We found no significant relationship between prevalence of gene mutation and pain ($P = 0.595$). As our patient had a *SOS1* mutation, we reviewed seven studies on *SOS1* genotype–phenotype correlations. Only one study by Smpokou et al. [2012] evaluated the prevalence of chronic pain by genotype. Twenty-three percent (8/35) of the study population had *SOS1* mutations. Among these subjects, 75% (6/8) had chronic joint pain, 50% (4/8) had chronic back pain, and 50% (4/8) had chronic muscle pain. In the remaining studies, chronic pain was not evaluated or reported [Roberts et al., 2007; Tartaglia et al., 2007 Ko et al., 2008; Narumi et al., 2008; Pierpont et al., 2009; Lepri et al., 2011]. In our study, 64% (7/11) subjects with *SOS1* mutations had pain. Consistent with the Smpokou et al. [2012] article, 71% (5/7) had joint pain and 43% (3/7) had back pain.

The results of our study confirm that pain is present among both the adult and pediatric populations alike. Fifty percent of subjects with chronic pain were children, specifically <16 years old. Smpokou et al. [2012] reported that chronic joint and back pains commonly originated in adulthood (age of onset 5–41 years for joints and 16–48 years for back); whereas, chronic muscle pain originated in childhood (age of onset 3–13 years). The authors did not comment on what percent of their subjects had pain onset in childhood.

In our study, location of pain was more common in extremities and joints compared to head, neck, trunk, and back ($P = 0.066$). Subjects with hypermobile joints were more likely to have pain ($P = 0.052$). Smpokou et al. [2012] reported high prevalence of joint hypermobility (49%) in their survey of NS subjects, a portion had chronic pain. These findings suggest that a common cause of chronic pain in NS is ligamentous laxity causing joint hypermobility, which parallels chronic pain etiology among heritable connective tissue disorders such as joint hypermobility syndrome (JHS) and Ehlers–Danlos syndrome, hypermobility type (EDS-HT). Nearly 30% of children with JHS/EDS-HT experience arthralgias, back pain, and myalgias; that rate increases to >80% among those over 40 years [Castori et al., 2011]. Individuals with these genetic disorders commonly have congenital capsuloligamentous laxity. Toddlers and children especially experience excessive motion of articular surfaces along non-physiologic directions [Hudson et al., 1998; Voermans et al., 2010]. Consequently, articular pain is caused by acute and recurrent, subclinical damage to joints, which results in dislocations and soft tissue injury. Castori et al. [2013] state that abnormal range of motion at a hypermobile joint can increase stress on adjacent muscles and tendons and activate nociceptive pain fibers. Nelson et al. [2014] surveyed 993 Marfan individuals and found that 67% suffered from chronic pain. The authors propose an etiology of pain similar to that of JHS/EDS-HT. Among JHS individuals, cervical hypermobility and Arnold–Chiari malformation are a cause of daily headache [Hall et al., 2008]. Our study population may have had a similar etiologies of headache and neck and back pain.

A rare feature of the NS spectrum is NS/MGCLS. Lesions frequently affect the jaws but can occur in other bones or soft tissues [Beneteau et al., 2009]. In our study, 4% (2/45) of subjects had NS/MGCLS. Both subjects had chronic pain and jaw cysts. They specifically experienced pain in their extremities and joints but not in their heads or jaws. Their pain may have been related to giant cell lesions in the extremities, and therefore, it may be a confounding factor in our analysis

We found that autoimmune diseases can be concomitant with RASpathies [Quaio et al., 2012]. In our study, swelling in extremities was not significantly associated with pain in joints or extremities. Two chronic pain subjects were evaluated by a rheumatologist and only one was formally diagnosed with autoimmune disease. This subject's joint and extremity pain may have been directly caused by an autoimmune process and inflammation. The low prevalence of confirmed rheumatologic disease may not accurately reflect our patient sample, as not all patients with pain were evaluated by a rheumatologist. The majority (86%) did, however, see a medical specialist who may have assessed them for rheumatologic disease.

Chronic widespread pain (CWP) is another possible cause of pain among our subjects. CWP is defined by the American College of Rheumatology as pain present in at least two contralateral quadrants in the axial skeleton, which persisted for at least three months [Croft et al., 1993; Hunt et al., 1999]. This pain syndrome is reported in 10% of the general population [Croft et al., 1993]. Eighty-six percent (24/28) of our subjects experienced pain in contralateral quadrants of the axial skeleton, and could by definition merit the diagnosis of CWP.

One patient reported osteoporosis and associated hip fracture; we did not specifically survey a diagnosis of osteoporosis. In our

remaining subjects with pain, previous trauma and fractures were unrelated to chronic pain. In 79% of pain subjects who had had surgery, the site of pain was unrelated to previous surgeries. Smpokou et al. [2012] reported that 14% of their NS subjects had osteopenia and osteoporosis starting as young as 17 years. Stevenson et al. [2011] concluded that osteoporosis and bone demineralization is more prevalent among Costello syndrome and neurofibromatosis type 1 and occurs at low rates among patients with NS. Thus, the majority of our study subjects likely had a different etiology of pain.

Our pain interference survey results indicated that pain interfered with subject mood at an average of 5 ± 3 on a scale of 1–10 (Table V). In 35 NS subjects, Smpokou et al. [2012] reported a 49% frequency of diagnosis and treatment for depression and/or anxiety including psychiatric counseling. Noonan [2005b] reported a 29% frequency of depression among 56 adults. Although, both studies had small sample sizes, these rates are higher than in the general population. The prevalence of major depression among the US adults is 6.7% and that of anxiety disorders is 18.1% [Kessler et al., 2005]. Mood may also be affected by seasonal weather patterns. More pain may be perceived when rainy and cloudy weather conditions cause depressed mood [Sulman, 1984]. We did not query subjects on concomitant psychological disease. Subject mood may have exacerbated their pain or the pain may have exacerbated their mood symptoms.

Chronic pain is a cause of fatigue by several mechanisms [Castor et al., 2013]. In our study pain interference survey results revealed that pain-affected subject sleep at an average of 6 ± 4. Tinkle et al. [2010] and Voermans et al. [2010] suggest that joint pain, periodic limb movements, and restless leg syndrome can interfere with sleep and can cause fatigue among EDS individuals. Another cause of fatigue is increased exertion required to chronically overcome joint instability in daily movements. EDS individuals have poor postural control due to hypotonia and lack of proprioception [Mallik et al., 1994]. Our NS study population may experience similar consequences of their chronic pain and joint hypermobility. Reciprocally, chronic fatigue caused by hypermobile joints, may contribute to depressed mood, which thereby increases the perception of pain.

We studied the alleviating and aggravating aspects of chronic pain such as climate zone of residence. For our patient, pain was temporarily alleviated by moving from a colder climate (northern Midwest) to a warmer climate (Southwest). Subjects anecdotally reported similar relationships between pain and climate. Eighty-three percent (15/18) of patients from cold climates experienced pain ($P = 0.004$).

Previous studies suggest, that weather changes cause contraction and expansion of tendons, muscles, bones, and scar tissue in different ways. Changes in barometric pressure and temperature increase joint stiffness and the sensitivity of nociceptive response, especially in inflammatory joints [Rasker et al., 1986; Besson and Chaouch,1987]. Severity of inflammatory chronic pain often fluctuates with weather. Rheumatoid arthritis patients experience worse pain under conditions of low temperatures and high humidity [Patberg et al., 1985]. Jamison et al. [1995] studied the effect of climate on severity of chronic pain in children and adults living in the four major US cities with various climates. Thirty-nine percent of the population had a diagnosis of arthritis. They found that individuals living in colder climates did not report higher pain scores, higher pain frequencies, or a greater influence of the weather on their pain. Rather, changes in weather, regardless of overall climate, were pain triggers. In our study, some patients anecdotally reported increased pain with changes in weather. We found a significant relationship between cold climate and pain. It is unclear whether the mechanism of pain of rheumatoid arthritis or the subjects in the Jamison et al. [1995] study is the same or different from the mechanism of pain among our study subjects.

We attempted to determine the prevalence of GH analgesia among NS individuals with chronic pain. One typical treatment for short stature in NS is GH. NS individuals may have either impaired GH release or GH resistance [Binder et al., 2005]. GH is not approved by the Food and Drug Administration for analgesia, but it has been shown to improve pain in fibromyalgia and Turner syndrome individuals and anecdotally in NS individuals [Amundson et al., 2010; Cuatrecasas et al., 2012]. The mechanism of pain relief is not well understood; it may be related to the analgesic effect of GH on the hippocampus and limbic cortex where pain is modulated and processed [Lathe, 2001; Cuatrecasas et al., 2012]. In our study, only 33% (15/45) of subjects reported treatment with GH. Among subjects without chronic pain, the prevalence of GH treatment was not significant ($P = 0.607$). However, this investigation was limited by the small sample size and collection of patient data at a single time point. Other than the patient in our case report, we did follow-up with subjects to assess if they had improvement over time with GH treatment.

CONCLUSIONS

Pain is a frequent and under-recognized clinical feature of NS. We found that it is a prevalent symptom in adults and children among a random sampling of NS individuals. In our population pain was significantly more prevalent in the extremities and joints and was associated with hypermobile joints. We found that chronic pain subjects experienced pain inference with their daily mood and activities. Chronic pain may be aggravated by colder climate, but further studies should be performed to confirm this. Although, 86% of subjects reported their pain to a specialist and 46% reported it to a medical geneticist, an etiology for their pain was rarely found. We did not find a relationship between GH treatment and a lack of pain; this analysis was limited by a small sample size. Our study was a preliminary investigation with the purpose of describing chronic pain in NS. Our study was limited by the sample; individuals attending the RASopathies conference may not be representative of the NS population. A more comprehensive, controlled prospective study should be done to evaluate the precipitating factors, presentations, age of onset, aggravating factors, alleviating factors, etiologies, and natural history of pain, as well as physical findings and treatments, including GH. This study should raise awareness about pain as a chronic symptom of NS among pediatric and adult populations. Geneticists and other physicians should inquire about symptoms of pain and treat it appropriately as part of routine health supervision for their patients with NS.

REFERENCES

Amundson E, Boman UW, Barrenas ML, Bryman I, Landin-Wilhelmsen K. 2010. Impact of growth hormone therapy on quality of life in adults with Turner syndrome. J Clin Endocrinol Metab 95:1355–1359.

Bader-Meunier B, Cave H, Jeremiah N, Magerus A, Lanzarotti N, Rieux-Laucat F, Cormier-Daire V. 2013. Are RASopathies new monogenic predisposing conditions to the development of systemic lupus erythematosus? Case report and systematic review of the literature. Semin Arthritis Rheum 43:217–219.

Beneteau C, Cave H, Moncla A, Dorison N, Munnich A, Verloes A, Leheup B. 2009. SOS1 and PTPN11 mutations in five cases of Noonan syndrome with multiple giant cell lesions. Eur J Hum Genet 7: 1216–1221.

Besson JM, Chaouch A. 1987. Peripheral and spinal mechanisms of nociception. Physiol Rev 67:67–186.

Binder G, Neuer K, Ranke MB, Wittekindt NE. 2005. PTPN11 mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. J Clin Endocrinol Metab 90:5377–5381.

Bufalino A, Carrera M, Carlos R, Coletta RD. 2010. Giant cell lesions in Noonan syndrome: Case report and review of the literature. Head Neck Pathol 4:174–177.

Castori M, Sperduti I, Celletti C, Camerota F, Grammatico P. 2011. Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers–Danlos syndrome, hypermobility type). Clin Exp Rheumatol 29:998–1005.

Castori M, Morlino S, Celletti C, Ghibellini G, Bruschini M, Grammatico P, Blundo C, Camerota F. 2013. Re-writing the natural history of pain and related symptoms in the joint hypermobilitysyndrome/Ehlers-Danlos syndrome, hypermobility type. Am J Med Genet Part A 161A: 2989–3004.

Cirstea IC, Kutsche K, Dvorsky R, Gremer L, Carta C, Horn D, Roberts AE, Lepri F, Merbitz-Zahradnik T, Konig R, Kratz CP, Pantaleoni F, Dentici ML, Joshi VA, Kucherlapati RS, Mazzanti L, Mundlos S, Patton MA, Silengo MC, Rossi C, Zampino G, Digilio C, Stuppia L, Seemanova E, Pennacchio LA, Gelb BD, Dallapiccola B, Wittinghofer A, Ahmadian MR, Tartaglia M, Zenker M. 2010. A restricted spectrum of NRAS mutations causes Noonan syndrome. Nat Genet 42:27–29.

Cleeland CS, Ryan KM. 1994. Pain assessment: Global use of the brief pain inventory. Ann Acad Med Singapore 23:129–138.

Cook KF, Dunn W, Griffith JW, Morrison MT, Tanquary J, Sabata D, Victorson D, Carey LM, Macdermid JC, Dudgeon BJ, Gershon RC. 2013. Pain assessment using the NIH toolbox. Neurology 80:S49–S53.

Croft P, Rigby AS, Boswell R, Schollum J, Silman A. 1993. The prevalence of chronic widespread pain in the general population. J Rheumatol 20:710–713.

Cuatrecasas G, Alegre C, Fernandez-Sola J, Gonzalez MJ, Garcia-Fructuoso F, Poca-Dias V, Nadal A, Cuatrecasas G, Navarro F, Mera A, Lage M, Peino R, Casanueva F, Linan C, Sesmilo G, Coves MJ, Izquierdo JP, Alvarez I, Granados E, Puig-Domingo M. 2012. Growth hormone treatment for sustained pain reduction and improvement in quality of life in severe fibromyalgia. Pain 153:1382–1389.

Furler L. 2013. Validity and reliability of the pain questionnaire "brief pain inventory". A literature research. Pflege Z 66:546–550.

Hall T, Briffa K, Hopper D. 2008. Clinical evaluation of cervicogenic headache: A clinical perspective. J Man Manip Ther 16:73–80.

Hudson N, Fitzcharles MA, Cohen M, Starr MR, Esdaile JM. 1998. The association of soft-tissue rheumatism and hypermobility. Br J Rheumatol 37:382–386.

Hunt IM, Silman AJ, Benjamin S, McBeth J, Macfarlane GJ. 1999. The prevalence and associated features of chronic widespread pain in the community using the 'Manchester' definition of chronic widespread pain. Rheumatology 38:275–279.

Jafarov T, Ferimazova N, Reichenberger E. 2005. Noonan-like syndrome mutations in PTPN11 in patients diagnosed with cherubism. Clin Genet 68:190–191.

Jamison RN, Anderson KO, Slater MA. 1995. Weather changes and pain: Perceived influence of local climate on pain complaint in chronic pain patients. Pain 61:309–315.

Kessler R, Chiu W, Demler O, Walters E. 2005. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Arch Gen Psychiatry 62:617–627.

Ko JM, Kim JM, Kim GH, Yoo HW. 2008. PTPN11, SOS1, KRAS, and RAF1 gene analysis, and genotype-phenotype correlation in Korean patients with Noonan syndrome. J Hum Genet 53:999–1006.

Lathe R. 2001. Hormones and the hippocampus. J Endocrinol 169: 205–231.

Lepri F, De Luca A, Stella L, Rossi C, Baldassarre G, Pantaleoni F, Cordeddu V, Williams BJ, Dentici ML, Caputo V, Venanzi S, Bonaguro M, Kavamura I, Faienza MF, Pilotta A, Stanzial F, Faravelli F, Gabrielli O, Marino B, Neri G, Silengo MC, Ferrero GB, Torrrente I, Selicorni A, Mazzanti L, Digilio MC, Zampino G, Dallapiccola B, Gelb BD, Tartaglia M. 2011. SOS1 mutations in Noonan syndrome: Molecular spectrum, structural insights on pathogenic effects, and genotype-phenotype correlations. Hum Mutat 32:760–772.

Mallik AK, Ferrell WR, McDonald AG, Sturrock RD. 1994. Impaired proprioceptive acuity at the proximal interphalangeal joint in patients with the hypermobility syndrome. Br J Rheumatol 33:631–637.

Narumi Y, Aoki Y, Niihori T, Sakurai M, Cave H, Verloes A, Nishio K, Ohashi H, Kurosawa K, Okamoto N, Kawame H, Mizuno S, Kondoh T, Addor MC, Coeslier-Dieux A, Vincent-Delorme C, Tabayashi K, Aoki M, Kobayashi T, Guliyeva A, Kure S, Matsubara Y. 2008. Clinical manifestations in patients with SOS1 mutations range from Noonan syndrome to CFC syndrome. J Hum Genet 53:834–841.

Nelson AM, Walega DR, McCarthy RJ. 2015. The incidence and severity of physical pain symptoms in marfan syndrome: A survey of 993 patients. Clin J Pain (Epub ahead of print).

Neumann TE, Allanson J, Kavamura I, Kerr B, Neri G, Noonan J, Cordeddu V, Gibson K, Tzschach A, Kruger G, Hoeltzenbein M, Goecke TO, Kehl HG, Albrecht B, Luczak K, Sasiadek MM, Musante L, Laurie R, Peters H, Tartaglia M, Zenker M, Kalscheuer V. 2009. Multiple giant cell lesions in patients with Noonan syndrome and cardio-facio-cutaneous syndrome. Eur J Hum Genet 17:420–425.

Noonan JA. 1968. Hypertelorism with turner phenotype. A new syndrome with associated congenital heart disease. Am J Dis Child 116:373–380.

Noonan J. 2005a. Noonan syndrome and related disorders. Prog Periodic Cardiol 20:177.

Noonan J. 2005b. Noonan syndrome. In: Goldstein S, Reynolds CR, editors. Handbook of neurodevelopmental and genetic disorders in adults. New York: Guilford Press. pp 308–319.

Patberg WR, Nienhuis RL, Veringa F. 1985. Relation between meteorological factors and pain in rheumatoid arthritis in a marine climate. J Rheumatol 12:711–715.

Pierpont EI, Pierpont ME, Mendelsohn NJ, Roberts AE, Tworog-Dube E, Seidenberg MS. 2009. Genotype differences in cognitive functioning in Noonan syndrome. Genes Brain Behav 8:275–282.

Quaio CR, Carvalho JF, da Silva CA, Bueno C, Brasil AS, Pereira AC, Jorge AA, Malaquias AC, Kim CA, Bertola DR. 2012. Autoimmune disease and

multiple autoantibodies in 42 patients with RASopathies. Am J Med Genet Part A 158A:1077–1082.

Rasker JJ, Peters HJ, Boon KL. 1986. Influence of weather on stiffness and force in patients with rheumatoid arthritis. Scand J Rheumatol 15:27–36.

Reinker KA, Stevenson DA, Tsung A. 2011. Orthopaedic conditions in Ras/MAPK related disorders. J Pediatr Orthop 31:599–605.

Roberts AE, Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, Li L, Yassin Y, Tamburino AM, Neel BG, Kucherlapati RS. 2007. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. Nat Genet 39:70–74.

Sarkozy A, Carta C, Moretti S, Zampino G, Digilio MC, Pantaleoni F, Scioletti AP, Esposito G, Cordeddu V, Lepri F, Petrangeli V, Dentici ML, Mancini GM, Selicorni A, Rossi C, Mazzanti L, Marino B, Ferrero GB, Silengo MC, Memo L, Stanzial F, Faravelli F, Stuppia L, Puxeddu E, Gelb BD, Dallapiccola B, Tartaglia M. 2009. Germline BRAF mutations in Noonan, LEOPARD, and cardiofaciocutaneous syndromes: Molecular diversity and associated phenotypic spectrum. Hum Mutat 30:695–702.

Sharland M, Burch M, McKenna WM, Paton MA. 1992. A clinical study of Noonan syndrome. Arch Dis Child 67:178–183.

Smpokou P, Tworog-Dube E, Kucherlapati RS, Roberts AE. 2012. Medical complications, clinical findings, and educational outcomes in adults with Noonan syndrome. Am J Med Genet Part A 158A:3106–3111.

Stevenson DA, Schwarz EL, Carey JC, Viskochil DH, Hanson H, Bauer S, Weng HC, Greene T, Reinker K, Swensen J, Chan R, Yang F, Senbanjo L, Yang Z, Mao R, Pasquali M. 2011. Bone resorption in syndromes of the Ras/MAPK pathway. Clin Genet 80:566–573.

Sulman FG. 1984. The impact of weather on human health. Rev Environ Health 4:83–119.

Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, Kalidas K, Patton MA, Kucherlapati RS, Gelb BD. 2001. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 29:465–468.

Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, Pandit B, Oishi K, Martinelli S, Schackwitz W, Ustaszewska A, Martin J, Bristow J, Carta C, Lepri F, Neri C, Vasta I, Gibson K, Curry CJ, Siguero JP, Digilio MC, Zampino G, Dallapiccola B, Bar-Sagi D, Gelb BD. 2007. Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. Nat Genet 39:75–79.

Tinkle BT. 2010. Joint hypermobility handbook—A guide for the issues & management of Ehlers–Danlos syndrome hypermobility type and the hypermobility syndrome. Greens Fork: Indiana Left Paw Press.

van der Burgt I. 2007. Noonan syndrome. Orphanet J Rare Dis 2:4.

Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. 2010. Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. J Pain Symptom Manage 40:370–378.

Verloes A, Caye A, Dieux Coeslier A, Baumann C, Vincent-Delorme C, Bouvagnet P, David A, Lacombe D, Blanchet P, Isidor B, Rio M, Héron D, Sauvion D, Alessandri JL, Drouin-Garraud V, Doray B, Pouvreau N, Cavé A, 2014. Noonan syndrome due to RIT1 mutations: Further clinical and molecular delineation in 32 cases (Abstract/Program #128). Presented at the 64th Annual Meeting of The American Society of Human Genetics, in San Diego.

Wolvius EB, de Lange J, Smeets EE, van der Wal KG, van den Akker HP. 2006. Noonan-like/multiple giant cell lesion syndrome: Report of a case and review of the literature. J Oral Maxillofac Surg 64:1289–1292.