



## Emotional experience in parents of children with Zellweger spectrum disorders: A qualitative study



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### ABSTRACT

Zellweger spectrum disorders (ZSDs) are rare, debilitating genetic diseases of peroxisome biogenesis that require constant management and lifelong care. Nevertheless, the experience of family caregivers for children diagnosed with ZSD is not well understood. In this study, we sought to characterize the emotional experience of ZSD family caregivers. Three 90-min focus groups were conducted with thirty-seven parents (25 mothers and 12 fathers) of children with ZSD during a family advocacy conference. Focus groups were arranged by age of proband (Group 1: 0–4 years, Group 2: 5–10 years, Group 3: > 11 years). Audio recordings of focus groups were transcribed and analyzed using software for coding purposes. Analyzed content was validated using peer debriefing, member checking, and method triangulation. Focus group results showed that nearly a third of ZSD caregivers described their overall emotional experience as a “rollercoaster.” Additionally, three interconnected themes were identified: 1) range of emotions, 2) stressors, and 3) coping. Feeling overwhelmed and devastated were the most frequently described emotional responses. Corresponding stressors to these emotions included the burden of caregiver tasks associated with ZSD, and negative interactions with healthcare professionals. The most common coping strategies were acceptance of limitations of the diseases, redefining “normal” in the parenting experience, and advocating on behalf of the child and the patient community. This study underscores the profound emotional impact on parents who are caregivers for children with ZSDs, highlighting the utility of patient community feedback and qualitative approaches to fully characterize the overall family experience. Simple, targeted approaches focusing on improved communication between healthcare professionals and families, as well as offering resources for emotional support may greatly improve the lives of families living with ZSD and other rare pediatric diseases.

### 1. Introduction

Zellweger spectrum disorders (ZSDs) are rare genetic diseases of peroxisome biogenesis with a cumulative incidence of ~1:50,000 births [1,2]. ZSDs are caused by mutations in *PEX* genes and result in defective peroxisome assembly and function. As peroxisomes are involved in critical metabolic pathways in nearly all cells of the body, ZSDs have

profound impact throughout fetal development and into adult life. Prominent clinical features seen at birth or developing during childhood including facial dysmorphism, hypotonia, psychomotor delay, visual impairment, deafness and seizures. Adrenal insufficiency [3], failure to thrive, and diminished bone mineral density [4] may develop over time. Neuro-regression is commonly seen. There is broad phenotypic and genetic heterogeneity in ZSDs, and wide variation in disease

*Abbreviations:* DBPD, D-bifunctional protein deficiency; GFPD, Global Foundation for Peroxisomal Disorders; ZSD, Zellweger spectrum disorders

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progression exists. Severely affected patients do not survive infancy or early childhood, whereas milder patients have a much longer lifespan with fewer complications, even surviving as adults [1,2]. The wide variation in disease severity and the multi-organ involvement in ZSDs complicates prognosis and medical management. Consequently, ZSD patients require constant and life-long care, thus placing significant physical, mental and emotional burden on caregivers. To date, however, the disease burden on caregivers remains poorly understood and is likely considerably underappreciated. An assessment of this burden is necessary to help evaluate the full societal impact of ZSDs.

Studies in chronic pediatric disease have highlighted the relationship between caregiver stress and patient outcomes (as reviewed in [5]). Recently, several studies have sought to identify the challenges and barriers faced by caregivers in the rare disease community [6–11]. For ZSD caregivers, however, information on their emotional status in relation to disease impact, in addition to their management and coping strategies to deal with personal and familial emotional stress, remains unknown. In short, data regarding the overall impact of caregiving for a child with ZSD on caregiver quality of life is lacking.

Qualitative methodology is particularly well-suited to research designed with an eye toward eliciting information that may not be easily garnered using surveys or questionnaires [12,13]. By using an individual's "own voice", this approach helps explain and interpret behavior employing process-driven research methodology that examines how and why individuals arrive at the choices they make rather than relying on researcher-based assumptions [13].

Here, our goal is to characterize the ZSD caregiver emotional experience in order to develop a comprehensive picture of the specific influences and interactions within a caregiver's daily life. Recognition of successful vs. unsuccessful approaches to daily care of their child will help to develop a more comprehensive framework of management guidelines that can benefit patients, caregivers and healthcare professionals who care for ZSD patients.

## 2. Materials and methods

### 2.1. Recruitment

Approval for the study was granted by the Montclair State University Institutional Review Board (IRB-FY16–17-529). All participants for this study were members of the Global Foundation for Peroxisomal Disorders (GFPD; <https://www.thegfpd.org/>). Initial recruitment sought feedback from ZSD families on data collection procedures and focus group interview questions during a conference call with the PI, the GFPD Board of Directors, and the GFPD Community Advisory Council. During this conference call, the purpose, goals, and format of data collection were described, including the approximate time involvement and the topics of questions that would be asked during the focus groups.

After finalization of the focus group interview guide, study recruitment fliers were posted on the GFPD website and Facebook page to solicit enrollment. Individuals self-selected to participate. Inclusion criteria was being a parent or family caregiver of a child (living or deceased) with a ZSD or a clinically-similar peroxisome disorder (including acyl-CoA oxidase deficiency or D-bifunctional protein deficiency). All recruited participants had confirmed genetic and/or biochemical diagnosis of their child via caregiver-report in the GFPD membership registry. In order to optimize description of the full range of caregiving perspectives, participation from a broad range of experiences was encouraged (deceased vs. living patient, recently diagnosed vs. multiple years since diagnosis).

### 2.2. Data collection

Data were collected using a demographic questionnaire and a semi-structured focus group guide. The demographic questionnaire gathered

information on age, race/ethnicity, geographical location, and family/household information. It included primarily multiple-choice questions designed to ensure that individual focus groups could be stratified according to demographic information and specific experiences.

The semi-structured focus group interview guide included a range of questions on issues relevant to the experiences of caregivers. The questions were divided into eight broad themes: 1) cognitive appraisal; 2) cognitive and behavioral coping mechanisms; 3) knowledge, attitudes and beliefs; 4) facilitators and barriers; 5) quality of life; 6) self-efficacy; 7) needs and resources; and 8) relationships (See Table 1 for complete focus group interview guide). To account for potential differences in responses based upon whether or not the child was living or deceased, some questions had two versions (Themes 2, 5, 7 and 8; above). One version used the phrase "if child has passed", and the other "if child is living".

Three focus groups (8–15 participants per group) were conducted on the same day during the bi-annual GFPD conference in July 2017. Each session lasted 90 min and was conducted in English. Sessions were audio- and videotaped. A member of the research team with extensive expertise in qualitative research techniques served as facilitator/moderator. Other members took notes on conversations or behaviors not fully captured during the discussions. The facilitator and assisting team members had no prior interactions with the participants. Notes taken by team members were shared with the facilitator during the session to highlight questions that required follow-up and also guided the research team in question revision during the focus groups when needed.

To reduce the risk of personal bias from the facilitator and encourage participant-to-participant interactions, the facilitator's role was limited to reading the questions, distributing response turns, and encouraging personal experience sharing. The individual themes were written on an easel pad to maintain focused discussions. Follow-up prompts to encourage further discussion were used when needed.

### 2.3. Data analysis

Focus group audiotapes were transcribed verbatim by a professional transcription company (Rev.com, San Francisco, CA). Alphanumeric designations were assigned to replace participants' names in the transcripts to ensure de-identification of data. Transcripts were reviewed and response patterns by the caregivers were noted, with particular focus on any misinterpretations of the intended meaning of the participants' words.

The transcripts were analyzed using a combination of deductive and inductive content analysis techniques [14]. A codebook was developed integrating common themes, as well as words and phrases that caregivers used to describe their own personal experiences. The final codes were catalogued in a qualitative software program (NVivo Pro version 11, QSR International Pty Ltd), and used to assign codes to participants' comments throughout each transcript. The codes were also assigned to text passages in the transcript files in Microsoft Word (version 15.34). The codes and corresponding comments were quantified by their frequency, referring to the number of times that a comment was categorized into a specific code, and extensiveness, referring to the number of participants that made comments that were categorized into a specific code [15]. For content validity, multiple techniques, including peer debriefing [16,17], member checking [18], and method triangulation [18] were used to ensure that the major themes and sub-themes were generated rigorously and systematically. These approaches served to reduce biases and comprehensively generate common themes and sub-themes of the caregiving experience among ZSD families [13].

## 3. Results

### 3.1. Demographic information

A total of thirty-seven subjects (25 mothers and 12 fathers)

**Table 1**  
Semi-structured focus group interview guide.

Theme	Sample questions
Cognitive appraisal	<ul style="list-style-type: none"> <li>● How would you describe your 'emotional experience', from caring for or having cared for a child with a peroxisome disorder?</li> <li>● Has your emotional experience changed over the course of your child's life? How?</li> <li>● If your child has passed, has your emotional experience changed since then?</li> <li>● Is there an aspect(s) of the caregiving experience that is most/least stressful or demanding? How and why?</li> </ul>
Cognitive and behavioral coping mechanisms	<ul style="list-style-type: none"> <li>● Throughout your child's life, do/did you feel that your role and responsibilities as a caregiver have changed or shifted over time? In what way, and why?</li> <li>● What do/did you <u>do</u> to cope (behaviors and activities)?</li> <li>● How do/did you cope emotionally?</li> <li>● If your child has passed, was there a point when you felt it was okay for life to be "normal" again? If yes, what does "normal" mean to you and when was that? If no, explain.</li> </ul>
Knowledge, attitudes and beliefs	<ul style="list-style-type: none"> <li>● On a scale of 1–10, 1 being 'none' to 10 being 'very good', how would you rate your understanding of the nature of the disease, in general? How do you feel about this rating? Explain why.</li> <li>● How would you rate your understanding of all available treatment options? How do you feel about this rating? Explain why.</li> <li>● How do/did you manage and prioritize the multiple needs of your child?</li> </ul>
Quality of life	<ul style="list-style-type: none"> <li>● How would you define the term 'quality of life'? What elements are included? What elements are not included?</li> <li>● How do/did you perceive your child's quality of life? Which aspects are affected the most and why? What measures have you taken to enhance his/her quality of life? Why or why not?</li> <li>● How do/did you perceive your own quality of life being a caregiver? Which aspects are affected the most and why? What measures have/had you taken to enhance your quality of life? Have/Had there been any changes? Why or why not?</li> <li>● How do/did you perceive your own quality of life if your child has passed? Which aspects are affected the most and why? What measures have you taken to enhance your quality of life since your child's passing? Have there been any changes? Why or why not?</li> </ul>
Self-efficacy	<ul style="list-style-type: none"> <li>● How do/did you feel about your 'ability' to take care of all your child's needs (confidence-level)?</li> <li>● Are there any areas that you feel more confident about? Why?</li> <li>● Are there any areas that you feel less confident about? Why?</li> <li>● Has your confidence level changed over time? What led to the change?</li> </ul>
Needs and resources	<ul style="list-style-type: none"> <li>● Describe, in your opinion, what makes a medical or health professional competent or qualified to address your child's needs related to this disorder.</li> <li>● Are there any medical/health issues related to this disorder that you believe are currently <u>not addressed well</u> by the medical community? If so, what are they? What do you think would make it better?</li> <li>● If your child has passed, are there any nutrition/growth issues related to this disorder that you believe were not addressed well by the medical community during their life but have <u>since improved</u>? If so, what are they?</li> <li>● What aspects of the disease and treatment do/did you need help with the most and why?</li> </ul>
Relationships	<ul style="list-style-type: none"> <li>● How do you think care could be/could have been customized or tailored more to your child's needs?</li> <li>● Do you feel that the diagnosis has changed your relationships with yourself, your spouse, other children, other children who are older and no longer living at home, other extended family members, and friends? In what way?</li> <li>● If your child has passed, do you feel that the death of your child has changed your relationships with yourself, and your spouse, other children who are older vs. younger, other children who are older and no longer living at home, other extended family members, and friends? In what way?</li> <li>● If your child has passed, do you feel that the death of your child has changed your other children's relationships with yourself, your spouse, with each other, with other extended family members, and friends? In what way?</li> <li>● Describe, what in your opinion, makes a family 'strong' or 'tight-knit'?</li> <li>● If your child is living, how would you describe your current family situation in these terms? Has anything changed since the diagnosis?</li> <li>● If your child has passed, how would you describe your current family situation in these terms? Has anything changed since their diagnosis? Since their passing?</li> </ul>

ZSD; Zellweger spectrum disorder.

representing 30 children with ZSD and 7 children with D-bifunctional protein deficiency (DBPD), a clinically-similar peroxisome disorder, participated in the study. Focus groups were arranged by age of proband (either current age or age at time of death for bereaved caregivers). A total of three focus groups were conducted: (Group 1: 0–4 years, Group 2: 5–10 years, Group 3:  $\geq 11$  years). Twenty-seven participants were parents of living children, 9 were parents of deceased children, and one parent had 1 living and 1 deceased child. Thirty-three parents had one affected child, and four had two affected children (See [Table 2](#) for full demographic information).

### 3.2. Thematic analysis of the overall ZSD caregiver emotional experience

Given the volume of data collected, we opted to focus primarily on the overall emotional experience of caregivers. Analysis of the data generated three discrete yet inter-related themes to describe the overall ZSD caregiver emotional experience: 1) range of emotions – the specific emotions experienced by the ZSD caregiver at a specific time, 2) stressors – the circumstances/interactions/events that triggered a specific emotion, and 3) coping – the cognitive and behavioral strategies employed to address these emotional experiences. Below, we provide

definitions and illustrations of the themes and sub-themes, which have been labeled using actual quotations in order to provide a more representative descriptive reconstruction of the participants' experiences.

#### 3.2.1. Theme 1 – Range of emotions

The focus group discussions began with the participants summarizing emotional experience and sharing their perspectives on the caregiving process. There was a large range of emotions and responses that tracked the journey of the ZSD caregiver ([Table 3](#)).

3.2.1.1. Sub-theme - "So many different emotions". Some emotions were more commonly reported than others, as identified by frequency (total number of times reported) and extensiveness (number of participants that described a specific emotion). We describe the most common emotions below. All reported emotions with supporting quotes are listed in [Table 3](#).

"We have a raised constant level of stress".

Most frequently reported were feelings of being overwhelmed, stressed, or anxious. Feelings of exhaustion were also just as frequently reported.

"Under the umbrella of a very devastating and destructive disorder".

**Table 2**  
Demographic information for participants.

Total	N	%
	37*	100.0
<b>Family Role</b>		
Mother	25	67.6
Father	12	32.4
<b>Age (years)</b>		
25–34	8	21.6
35–44	24	64.9
45–54	3	8.1
55–64	2	5.4
<b>Ethnicity</b>		
White	35	94.6
Asian	2	5.4
<b>Marital Status</b>		
Single	1	2.7
Married	35	94.6
Divorced	1	2.7
<b>Highest Education</b>		
Technical	4	10.8
High School Grad	3	8.7
Some College	8	21.6
Bachelor's	12	32.4
Grad/Professional Degree	10	27.0
<b>Employment Status</b>		
Self-Employed	1	2.7
Unable to work	2	5.4
Part-Time	8	21.6
Full-Time	17	46.0
Not seeking employment	2	5.4
Homemaker	5	13.5
Student	1	2.7
Military	1	2.7
<b>Household Income (\$)</b>		
10–29 K	3	5.4
30–49 K	3	8.1
50–69 K	7	18.9
70–89 K	8	21.6
> 90 K	16	37.8
Decline	1	2.7
<b>Region of Residence</b>		
Midwest	7	18.9
Northeast	10	27.0
Southeast	10	27.0
Southwest	2	5.4
West	2	5.4
Outside US	4	10.8
<b>Peroxisome Disease of Child(ren)</b>		
ZSD	32	78.4
DBPD	5	16.2
<b>Number of Affected Children</b>		
1	33	10.8
2	4	94.6
<b>Status of Child(ren) (Alive/ Deceased)</b>		
Alive	27	67.6
Alive and Deceased	1	2.7
Deceased	9	24.3
<b>Age Range of Affected Children (years)</b>		
< 1	6	13.5
1–4	13	35.1
5–7	7	16.2
8–10	4	10.8
14–17	3	8.1
> 18	3	8.1
8–10, < 1*	1	2.7

**Table 2 (continued)**

Total	N	%
	37*	100.0
<b>Number of Unaffected Children</b>		
0	13	35.1
1	16	43.2
2	4	10.8
3	4	10.8

\* One caregiver had 2 children with ZSD in two different age ranges. ZSD; Zellweger spectrum disorder, DBPD; D-bifunctional protein deficiency.

**Table 3**  
Sample quotes for range of emotions in ZSD caregivers (Theme 1).**Stress**

*“There are many times during the day that I feel like I just, like, how can I possibly do all these things I have to do to keep you happy and healthy?”* – Mother to 4-year old with ZSD

*“I’m in a permanent state of anxiousness.”* – Mother to 3-year old with ZSD

*“I’m kind of stuck between overwhelming and exhausted.”* – Mother to 17-year old with ZSD

**Devastation**

*“My experience was gut-wrenching.”* – Bereaved mother to 7-year old with DBPD

*“There are some moments you want to cry all day.”* – Father to 3-year old with ZSD

**Anger**

*“And what’s frustrating is when they’re all in the same institution and they have electronic records that are made and designed to do that.”* – Mother to 4-year old with ZSD

*“Their coordination care is just awful. Impossible. It’s literally impossible. And if you get cancer or have cardiac issues, it’s like the jackpot. You know, they’re cutting edge. And it’s hard for me not to be so angry about that.”* – Father to 5-year old with ZSD

**Guilt**

*“Because they won’t do cochlears, now my daughter can’t speak anymore. I’ll never forgive myself for that, or anyone either.”* – Father to 5-year old with ZSD

*“Was it this, was it that? So that was an emotional rollercoaster because you always wonder is there something that can be done, and it’s just not being found out?”* – Mother to 17-year old with DBPD

**Fear**

*“But there’s a lot of fear too, because you know that where the path is gonna be.”* – Father to 5-year old with ZSD

*“Like she’s perfectly fine and then an hour later she’s just gone, like there’s nobody in there. And she’s just a limp rag and we don’t know what to do.”* – Mother to 5-year old with ZSD

**On diagnosis (Age of proband: 0–4 years)**

*“As devastating it is, I did feel peace and could let go of the blame, the self-guilt.”* – Mother to 3-year old with ZSD

**On clinical research participation (Age of proband: 9–35 years)**

*“It’s not going to fix her.”* – Mother to 35-year old with ZSD

**Feeling numb (Bereaved parents)**

*“I just shut down. I didn’t share anything. It was sort of like I didn’t feel.”* – Bereaved mother of 4-month old with DBPD

Included sample quotes were chosen to reflect responses from all focus groups.

\* Sample quotes reflecting the most common emotional response based on frequency (number of comments) and extensiveness (number of participants making comments). ZSD; Zellweger spectrum disorder, DBPD; D-bifunctional protein deficiency.

Extensively, participants described caregiving as a “gut-wrenching” or “devastating” experience that consumed their entire lives. Feelings of anger and frustration were also common, which were often directed at medical professionals or the healthcare system. One caregiver felt that their doctors were more concerned with treating a large number of

patients and not invested in learning more about ZSD or other rare diseases. Lack of coordination among the medical care team was a common complaint that triggered feelings of frustration and anger (See Theme 2).

*“So much personal blame, guilt”.*

Feelings of guilt and regret were reported by several participants. While some discussed feeling guilty about not being able to spend enough time with their non-affected children, a few expressed feelings of regret, which ranged from guilt over their child's challenges prior to diagnosis to spending too much time on fruitless or ill-advised medical consultations (Table 3).

Some emotions appeared to be specific to certain demographic characteristics found in each group. For example, relief was described in Group 1 (Age of proband: 0–4 years), primarily in response to receiving a diagnosis following a prolonged diagnostic process, while resignation and numbness were described in caregivers of older children and bereaved caregivers, respectively (Table 3).

3.2.1.2. *Sub-theme - “It's a rollercoaster”.* Participants revealed that

caregiving for a child affected with ZSD is an ongoing process that requires them to be prepared at all times. However, the emotional experience associated with caregiving was not static and changed based on what stressors were present at that point. Twelve out of the 37 participants described their emotional experience as a “rollercoaster”, referring to feelings oscillating between very positive to very negative emotions. Various caregivers identified the multiple emotions and how the emotions changed back and forth or progressed over time. Although both positive and negative emotions were reported, the majority of the positive emotions appeared to stem from coping strategies that caregivers employed to manage their emotional experience (See Section 3.2.3).

### 3.2.2. Theme 2 – Stressors

Participants discussed the various circumstances, interactions, or events that triggered specific emotions that characterized their caregiving experience. For the purpose of this study, we define these as stressors. Numerous stressors contributed to the emotional experience in ZSD caregivers (Table 4).

**Table 4**

Sample quotes for stressors contributing to ZSD caregiver emotional experience (Theme 2).

#### **“You have so much going on at any given time” (Managing caregiving tasks)\***

*“I am constantly re-prioritizing because everything is changing so much, and you have so much going on at any given time. Anything can happen, and then what was number two is now number five, and this one has merged into this one, and it's just this ongoing in my head, and it doesn't go away and you are always re-shifting things.”* – Mother to 17-year old with ZSD

*“My attention can only focus on like one or two things at a time that I like, forget the other things.”* – Mother to 3-year old with ZSD

*“It's a constant stress. [My son] doesn't eat”* – Mother to 1.5-year old with ZSD

*“It was devastating. Couldn't get out of bed, it just felt like I had failed as a mom, I couldn't feed my child.”* – Mother to 3-year old with ZSD

*“A lot of kids go through food intolerance and pain with feeding, and I don't know if it's just something that hasn't been figured out yet, a lack on nutritionists or just a lack of understanding of the illness.”* – Bereaved mother of 4-year old with ZSD

#### **“I felt like nobody was listening to me”: (Negative interactions with health care providers)**

*“I handed [the doctor] her card and I said she would like to talk to you about this, to tell you why it's adrenal insufficiency. He tossed it back at me and said ‘I've been doing this for forty years, and I know more than you.’”* – Mother to 9-year old with ZSD

*“When [my son] was first diagnosed, a geneticist told us the news and just handed us some pamphlets, and that was basically it. ‘I can't do anything. Read this pamphlet.’ Yeah, and ‘figure it out.’”* – Father to 4-year old with ZSD

*“We were diagnosed, and they handed me a piece of paper and sent me out the door.”* Mother to 3-year old with ZSD

*“Even though we have a great children's hospital, the lines of expertise are there, they don't like to talk to each other.”* – Bereaved father of 7-year old with DBPD

*“We have an incredible children's hospital. We have only a couple of doctors, two, three? Their coordination of care is just awful”* – Father to 5-year old with ZSD

*“There are so many specialists that have no bedside manner, and just the words they use when you're like ‘You're talking about my terminally ill child.’”* – Mother to 1.5-year old with ZSD

*“[The doctor] said, ‘Mourn all hopes and dreams you have for your child, because he's not going to survive the year.’ And so, for the next three months, I was sick. I was having constant panic attacks.”* – Mother to 1.5-year old with ZSD

#### **“It will impact every close relationship you have”: (Lack of support/understanding from family/community)**

*“People who don't do it, don't know what it's like.”* – Mother of 23-year old with ZSD

*“Well other parents with typically developing children, they don't understand our daily routine. They don't get that we have to go to the doctors three times a week.”* – Mother of 3-year old with ZSD

*“When you've got a child with such kind of disease, who are your real friends?” And you come to the conclusion you have not a lot of friends. And that is really hard.”* – Father to 3-year old with ZSD

*“I hate when people are like, ‘Well when will he stop seeing?’ I don't know. Or, ‘How much longer do you expect [your child] to be with you?’ I don't know.”* – Mother of 9-year old with ZSD

*“I told someone, ‘Stop putting me a pedestal because you know I have horrible days too’”* – Mother of 35-year old with ZSD

*“Having no support, you don't have any family, so it's always me.”* – Mother of 5-year old with ZSD

#### **“The worst part is not knowing” (Not knowing course of disease/ no natural history)**

*“The worst part is not knowing. Not knowing how long we have. Not knowing where we're going or if he's going to make it to fifth grade”* – Mother of 3-year old with ZSD

*“Just suddenly, like she's perfectly fine and then an hour later she's just gone, like there's nobody in there. And she's just a limp rag and we don't know what to do.”* – Mother of 5-year old with ZSD

*“We were very confused. Because it seemed like nobody knows what's going on.”* – Bereaved father of 6-month old with DBPD

#### **“So I have a death sentence now for my kid” (Impact of disease on child)**

*“And to see what she used to do (crying). She walked everywhere. And now, she sits in front of the TV and plays with a book, and that's it (crying). That's the hardest part.”* – Mother of 35-year old with ZSD

*“I made a cute video of [my child] on Facebook. And she's singing a song. And that's so meaningful to me now because she doesn't sing anymore. She barely talks anymore.”* – Mother of 23-year old with ZSD

*“He had a vision change a few years ago, and it was rapid when it happened. In less than nine days, I noticed when he was hitting and running into things that he normally would have memorized”* – Mother of 17-year old with ZSD

*“It's the same for every single parent in this room, and every single kid. And you'd have to watch it, and you know what's gonna happen. And you can't stop it. There's not a second that goes by that I don't think about that.”* – Father of 5-year old with ZSD

*“[Our child] is still growing and developing...yet I know where we're gonna end up. That's what the progression looks like.”* – Father of 5-year old with ZSD

#### **“The siblings of our kids are amazing. But what kind of life do they have?” (Impact of disease on other children)**

*“Yeah, [my healthy child is] seven years old and does his own laundry, makes his own food, and I feel terrible.”* – Mother of 9-year old with ZSD

*“The part that really hurts is actually figuring out how to manage with going to a ball game for [my healthy child] because [my affected child] can't be out in the sun or out in the heat, and so we feel it's kind of unfair for her”* – Mother of 9-year old with ZSD

*“It's very demanding, and it takes a lot away from the time we could have together and the time that I have with my unaffected daughter.”* – Mother of 1.5-year old with ZSD

Included sample quotes were chosen to reflect responses from all focus groups.

\* Most common stressors based on frequency (number of comments) and extensiveness (number of participants making comments). ZSD; Zellweger spectrum disorder, DBPD; D-bifunctional protein deficiency.

3.2.2.1. *Sub-theme - “You have so much going on at any given time”*. One of the most extensively reported stressors was managing the multiple needs of their child. Within this discussion, many participants shared their experience over not being able to manage their child's food and nutritional needs adequately. One mother stated that she felt that she “had failed as a mom” due to being unable to feed her child (Table 4).

3.2.2.2. *Sub-theme - “I felt like nobody was listening to me”*. The most frequently reported stressor was caregivers' experience when interacting with health care providers. Caregivers recounted events where health care providers were either unwilling to learn about the disorder or unwilling to work with the families to explore disease management options. Lack of care coordination across specialists, as well as a lack of empathy when conveying sensitive information to families were recurrent stressors in all three focus groups (Table 4).

3.2.2.3. *Sub-theme - “It will impact every close relationship you have”*. In discussing the importance of social networks, some individuals highlighted the contrasts between parents with and without children affected by ZSD. A perceived lack of adequate support and understanding, especially from family and friends, negatively affected caregivers' relationships with these individuals, and contributed to feelings of resentment, anger, and isolation among some participants (Table 4).

3.2.2.4. *Sub-theme - “The worst part is not knowing”*. Throughout the discussions, there were several comments that conveyed the participants' fear and confusion over the uncertainty of how the progression of the disease will specifically affect their child (Table 4).

3.2.2.5. *Sub-theme - “So I have a death sentence now for my kid”*. Despite the confusion and uncertainty, participants expressed deep sadness and

**Table 5**

Sample quotes for coping strategies used by ZSD caregivers (Theme 3).

<p><b>For better or for worse, our family has its own normal<sup>†</sup>(Cognitive)</b></p> <p>“We say normal for [our child] all the time. Like, no, those aren't normal, but they're normal for [him].” – Mother of 17-year old with ZSD</p> <p>“And it just becomes normal. I think establishing normal is part of coping.” – Father of 6-year old with ZSD</p> <p>“I mean we're trying to give [our son] every normal experience as possible. We took him skiing this year, like, I never thought I'd ever go skiing with him. So just trying to give him what every other five-year-old is experiencing in a way he is able to experience, it is really important to us. Really important to us. And it also helps us feel a little bit normal too.” – Mother of 4-year old with ZSD</p> <p>“We get a lot of stares with [our child] still drinking from a bottle, and she's four, and I'm like, you know what? If this is like the worst thing, so what?” – Mother of 4-year old with ZSD</p> <p>“Now I look back and I'm like, “That feeding tube was like the best thing we ever did.’ We do the 20 minute feed, and then we're off to play. ” – Mother of 3-year old with ZSD</p> <p>“It took us a lot of time to get to the point where we kind of said if we had [our child] 30 more minutes, or 30 more years, we are happy.” – Mother of 35-year old with ZSD</p> <p>“Because we have to live every day as it is on our only day. And that's a gift because you don't waste life” – Mother to 38- and 19-year old with ZSD</p> <p>“You appreciate everything more. Your time, your relationships the moments with your child...” – Bereaved mother of 4-year old with ZSD</p>
<p><b>I think we have a little cocoon...we support one another (Cognitive)</b></p> <p>“I think my support system was always my mother and a very close friend.” – Mother of 35-year old with ZSD</p> <p>“Things that [my partner] is really good at that I'm not great at, and [my partner's] mom is really involved in [our child's] care, so, in that way we're lucky.” – Mother of 3-year old with ZSD</p> <p>“But in terms of knowledge, I think I've learned more from [the GFPD] and other parents than any doctors that are specialists.” – Bereaved mother of 6-month old with DBPD</p> <p>“It comes from this group, where hearing from other families around what's worked, what hasn't worked, or try this therapy, try this treatment, or try this equipment. I would say everything, where [my son] is today, really has to do with this group.” – Mother of 4-year old with ZSD</p> <p>“Doctors that are willing to work together. And make a good team. Because that's what our kids need is a team. A doctor's not going to fix them or help them. So collaboration is a big, big thing.” – Bereaved mother of 4-year old with ZSD</p> <p>“Our genetic counselor basically set up all of our specialists and we met back with her every year, and it was just continuous. It said these are the ones you need to check with first and see who to follow up with. We had a really, really, amazing team. Really, really amazing.” – Bereaved father of 4-year old with ZSD</p> <p>“His general pediatrician is probably the most positive amazing wonderful person that we see. She's encouraging, she has fought for us. She knows that I'm not just like this crazy mom. She knows that if I call her, that it's for good reason. She listens to me and understands me, and I think that that makes such a big difference.” – Mother of 1.5-year old with ZSD</p>
<p><b>You have to be your child's advocate** (Behavioral)</b></p> <p>“You do have to build a team that is supportive of you,” – Mother to 38- and 19-year old with ZSD</p> <p>“Because I'm going to fight for education and I'm going to fight for doctors, and I'm going to fight, because my son deserves the best while he's here. My kid deserves just as much as anybody else's kid.” – Mother to 3-year old with ZSD</p> <p>“I am very picky about doctors. I think that you have to find the right doctor for you” – Mother to 17-year old with ZSD</p> <p>“Use [our child] to change the world just a little bit.” – Mother to 3-year old with ZSD</p> <p>“And then meeting with our congressmen, ‘What can we do?’ There has to be a reason that they gave us [our child]. There has to be. We have to find the silver lining in this, and so, a lot of our coping is expounding.” – Mother to 3-year old with ZSD</p>
<p><b>And we're just going to...do things that she likes to do(Behavioral)</b></p> <p>“I just think that it is really important that the kids to make decisions for themselves because if you look at their whole life, it's all controlled by other people. Because, you know they want to have input, they want to have a little bit of control over something in their life, and if you don't let them have it, it would make them real unhappy I would think.” – Mother of 23-year old with ZSD</p> <p>“And not force her. Like there's days she won't eat. Okay, don't eat today. But the next day, you can't fill her up. She eats all the time, so we don't-we just you know, go by her. Go by her.” – Mother of 35-year old with ZSD</p> <p>“And she will only wear one hearing aide. She will not wear both, even though she should. She won't wear her stretching thing. And sometimes I get frustrated, I'm thinking, maybe this stuff would help her but then I think well, if she doesn't want to do it, she's no going to, and what's the fight? You know, it's her decision.” – Mother of 17-year old with DBPD</p>
<p><b>You have to take time for you (Behavioral)</b></p> <p>“I feel like I kind of say here's my permission at these times, so that I can get through the things I need to do at other times.” – Mother to 5-year old with ZSD</p> <p>“I [am] reading a self-help book, a second self-help book actually. I read recently to take a note pad and draw two columns, and go what are you doing for everybody else, and what are you doing for yourself? And look at how they are balanced out.” – Mother to 17-year old with ZSD</p> <p>“We started counseling as soon as she was diagnosed, and been in it for four and a half years now. We don't plan on stopping any time soon.” – Bereaved father of 4-year old with ZSD</p>

Included sample quotes were chosen to reflect responses from all focus groups.

\* Most common cognitive coping strategy based on frequency (number of comments) and extensiveness (number of participants making comments).

\*\* Most common cognitive behavioral strategy based on frequency (number of comments) and extensiveness (number of participants making comments). ZSD; Zellweger spectrum disorder, DBPD; D-bifunctional protein deficiency; GFPD; Global Foundation for Peroxisomal Disorders.

concern over the overall progressive nature of the disease and the present (and anticipated) negative impact on the quality of life of their child (Table 4).

**3.2.2.6. Sub-theme - “The siblings of our kids are amazing. But what kind of life do they have?”** Additionally, participants expressed regret and guilt over the negative impact caregiving had on the time spent with and overall quality of life for their unaffected children (Table 4).

### 3.2.3. Theme 3 – Coping

In reflecting on their ability to address their child's needs, the impact of the caregiving experience on the family, and the resources currently available to them, participants discussed the personal strategies they adopted to cope with their responsibilities as parents of a child with ZSD. These strategies included both cognitive (changing thinking/perspective) as well as behavioral approaches (changing actions) (Table 4).

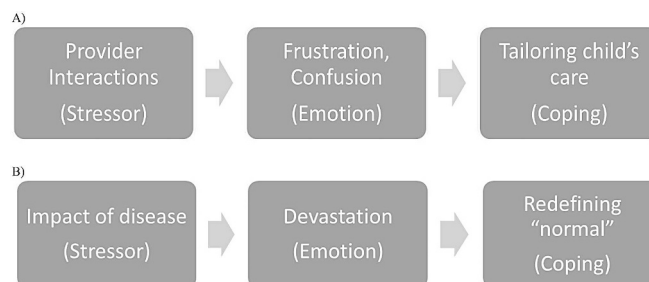
**3.2.3.1. Sub-theme - “For better or for worse, our family has its own normal”.** Caregivers most frequently and extensively discussed the importance of learning how to re-define their expectations of what constitutes a typical way of life for a parent/family of a child affected with ZSD. A recognition and acceptance of differences in parenting a child with ZSD (in contrast to parenting a typically developing child) was important in helping parents cope with the challenges and limitations of the disease and overall caregiving experience. Some parents felt that it was important to appreciate the caregiving experience, rather than dwell on the shortcomings. One mother, who expressed that although she initially felt as a “failure” for being unable to feed her child, later appreciated the convenience of a gastrostomy tube for feeding, stating “Now I look back and I'm like, ‘That feeding tube was like the best thing we ever did.’ We do the 20-minute feed, and then we're off to play.” (Table 5).

**3.2.3.2. Sub-theme - “I think we have a little cocoon...we support one another”.** For many parents, having a social support system seemed to be a crucial element in helping them manage their overall emotional experience. Several participants discussed the importance of advocacy organizations, the GFPD in particular, and its role in enhancing their knowledge and ability to address their child's needs more effectively. The medical community was also an important part of the caregiver social network. Attributes such as transparency, honesty, consistency, optimism, and a collaborative spirit fostered trust and respect in the health care provider, and subsequently had a positive impact on the caregiver emotional experience (Table 5).

**3.2.3.3. Sub-theme - “You have to be your child's advocate”.** During the discussions, participants talked about the various action-oriented, or behavioral, strategies they adopted to cope with the everyday challenges of the caregiving experience. These ranged from advocating for health care and disease management that was tailored to the needs of the child (most frequent and extensive behavioral coping strategy) to becoming more involved in promoting awareness about the disease (Table 5).

**3.2.3.4. Sub-theme - “And we're just going to...do things that she likes to do”.** Many participants, particularly parents of older children (Group 3: age of proband  $\geq 11$  years old), discussed the importance of allowing the child to make his or her own decisions and thus feel more empowered and have an improved quality of life (Table 5).

**3.2.3.5. Sub-theme - “You have to take time for you”.** Several participants openly and honestly shared the occasional need to “check out” or disconnect, or engage in activities that promote rest, rejuvenation, or personal growth, such as family counseling or reading books about managing stress (Table 5).



**Fig. 1.** Proposed framework for ZSD caregiver emotional experience. Tentative framework connecting themes of emotions, stressors and coping that were identified in qualitative analysis. A) Negative interactions with healthcare providers were categorized as a sub-theme under the “stressors” theme. This specific stressor appeared to trigger frustration and confusion (sub-theme under “emotions” theme), which could be addressed by caregivers taking an active role in their child's care (sub-theme under “coping” theme). B) The impact of the disease on the child (sub-theme under “stressors”) appeared to be related to feelings of devastation (sub-theme under “emotions”). These may be addressed by family caregivers cognitively focusing on being in the moment with their family and redefining their perspective on parenting a child with ZSD. ZSD; Zellweger spectrum disorder.

## 4. Discussion

This study is the first to address the impact of ZSD on caregivers with a focus on the overall emotional experience of parents of children diagnosed with ZSDs. Nearly a third of the study participants described their experience as a rollercoaster, referring to emotional responses changing rapidly throughout their caregiving experience. Feeling overwhelmed and devastated were the most frequent and extensively described emotional responses. Emotions were triggered by various stressors including the multitude of tasks associated with being a caregiver for a child with ZSD, and the interactions with professionals providing care to their children. Common coping strategies to manage the caregiver's emotional experience included acceptance of limitations of the diseases, redefining “normal” in the parenting experience, and advocating on behalf of the child and the patient community to achieve optimal care for their affected child.

Several studies have modeled the relationship between emotions, feelings, specific stressors and coping mechanisms [19,20]. A similar approach was used in our study in order to better understand how the ZSD caregiver emotional experience manifests, and identify points for potential intervention. For example, our analysis and subsequent proposed framework (Fig. 1) suggests that feelings of anger, frustration, and confusion (emotions) experienced by the caregiver related to negative interactions with healthcare providers (stressors) can be addressed by taking an active role in their child's care (coping strategy) (Fig. 1A). In another example, we observed that feelings of devastation (emotion) that were triggered by the impact of the disease on the child (stressor) were addressed by cognitively focusing on what their child *could* accomplish, being in the moment with their family, and appreciating the experience of being the parent to a child with ZSD (coping strategies)(Fig. 1B). For a complete table of these proposed relationships between specific emotions, stressors, and coping strategies, as well as supporting quotes, see Appendix A.

### 4.1. Implications of the study

While this is the first study looking at the impact of ZSD on the caregiver, the findings from this study echo findings among caregivers for other rare pediatric diseases. Caregivers of children with osteogenesis imperfecta, mucopolysaccharidosis, juvenile idiopathic arthritis, and early onset scoliosis describe their emotional experience as a roller coaster [11,21,22] and express feelings of devastation, sorrow, guilt, frustration and anxiety [6,21,23]. A recent review of studies

observing caregivers of rare diseases also reported similar emotions [24]. Studies looking across multiple rare diseases reported high psychological impact of rare disease on caregivers [8,10].

In our study, the burden of tasks associated with caregiving, such as dietary management, was a common stressor. One mother in our study described coming to terms with g-tube placement in the context of maternal identity. A 2012 qualitative meta-analysis [25] on tube feeding found similar sentiments in mothers, suggesting the need for more preventive psychological guidance in redefining parental identity in the face of pediatric feeding disorders. Our findings support this assertion.

Our study as well as others have reported negative interactions between caregivers and healthcare providers when managing care for their child [8,10]. Struggles with inclusion of parent input in care planning, as well as difficulties in care coordination across specialists have been reported among parents of children diagnosed with inherited metabolic disorders [8]. A recent study found that pediatricians experience difficulty and uncertainty when providing care for children with rare diseases due to lack of training and peer support [26]. These circumstances may contribute to the perceived negative interactions between families and healthcare providers, suggesting a strong need for resources aimed at facilitating better training, support networks, and education in rare disease for physicians. Furthermore, development of expertise, empathy, and knowledge of support resources in healthcare providers may help improve the overall rare disease caregiver experience. One study reported positive interactions between family caregivers and medical professionals with expertise in disease-specific care [10]. Recognition of positive and supportive professional networks as a coping strategy for ZSD caregivers was also an important theme for our study.

In our study, participants expressed regret and guilt over the negative impact caregiving had on their additional children that were not diagnosed with ZSD. A 2015 study found that siblings of children diagnosed with various rare diseases experienced complex emotions in the context of disease implications, family life and social life [27]. Our findings on the caregivers' emotions regarding the sibling impact of ZSD support that there is a need for further investigation and characterization of the sibling experience in ZSD and other rare pediatric diseases.

Collectively, this study and others suggest that despite differences in symptoms and clinical presentations in various rare pediatric disorders, there are similarities in rare disease caregiver experiences that are often triggered by similar circumstances across diseases. Additionally, given these similarities, it is likely that ZSD caregivers have shared needs with other rare disease caregivers. Shared needs for supportive care across caregivers for multiple rare diseases was emphasized in a recent report by Pelentsov et al [9]. Our study suggests that more support (social, emotional and physical) from the surrounding community may be useful in alleviating the burden of caregiving. Additionally, education, awareness, and sensitivity guidance for medical professionals may be useful in minimizing undesirable interactions between medical professionals and families.

Our study found that changes in the caregiver's perception of their family life was a common coping strategy to minimize the emotional impact of ZSD. This strategy, particularly redefining what the "normal" parenting experience means, has been reported in other rare pediatric diseases as well [7,28]. Identifying this cognitive change may be useful in the development of resources to help facilitate this change of mindset. For example, emotional support groups as well as professional psychological interventions targeting approaches to bring about these cognitive changes among caregivers may be important resources in the management of ZSD. A recent study reported that a pilot psychosocial support program in caregivers of cystic fibrosis decreased anxiety, fear of disease progression, and improved quality of life [29]. Additionally, a recent review found that certain cognitive-behavioral therapies may be useful in reducing parental stress and improvement of mental health

among parents of children with chronic illnesses. [30]. Similar programs or behavioral therapies could prove useful to ZSD caregivers.

#### 4.2. Study strengths

This study is the first of its kind studying ZSD caregivers. It encompassed both male and female caregivers, an important consideration as it has been recently demonstrated that the nature of caregiving in rare pediatric diseases may be influenced by gender [9]. Future analyses of these data will more deeply assess the role of gender in caregiving for ZSD.

Despite similarities in emotional experiences across other rare pediatric diseases, this is one of the first studies observing the emotional experience of caregivers of children with a rapidly progressive disorder that is often fatal, with considerable neurological and sensory impact and very few treatment options. These experiences are distinct from other studies in rare pediatric diseases, and resulted in additional emotions not previously described, such as grief and fear associated with loss of skills and the anticipated death of their child.

Additionally, this study incorporates the emotional experience of both current caregivers and bereaved caregivers, as well as specific experiences in distinct age groups of the patients, which likely provides a more comprehensive understanding of the overall ZSD caregiver journey.

To our knowledge, this is one of very few qualitative reports on the emotional experience of rare disease caregivers in the United States. A recent initiative from the National Alliance for Caregiving reported on the experiences of the rare disease caregivers in the U.S. This report found that more follow up and information on the caregiver experience as part of the overall body of literature on rare diseases is urgently needed [31]. Reports such as our study will hopefully foster better communication of needs and overall understanding between rare disease families and their medical care providers.

#### 4.3. Study limitations

Although recruitment efforts were targeted to include participants from a diverse population of ZSD families, demographic characteristics (including ethnicity, education and socioeconomic status) were fairly homogeneous with the exception of gender. Although a broad range of topics were discussed in the focus groups, there may be additional issues of importance to ZSD caregivers that were missed given the demographic similarities across the groups. Future recruitment efforts in such studies will need to be further targeted to ensure inclusion of participants from a variety of backgrounds. Additionally, the cross-sectional design of the study made it challenging to clearly determine the change in emotional experience over a given period, the role of a specific stressor over another on overall emotional experience, as well as the impact of coping strategies.

#### 4.4. Future studies

We will continue to identify more specific needs and experiences for ZSD caregivers across variables such as caregiver gender, bereaved status, and available resources. Future studies using more longitudinal approaches will serve to better define the direct impact of stressors and coping strategies on the ZSD caregiver emotional experience. Additionally, more targeted focus groups to better characterize the concept of quality of life in ZSD caregivers and patients will aid in the development of more quantitative tools to fully understand the impact of ZSD on a family.

## 5. Conclusion

Overall, the study emphasizes the need for clinicians, educators, and



policymakers involved in rare pediatric disease to take in account the experience of ZSD caregivers for disease management, development of educational materials and resource allocation. The study further gives previously unrecognized evidence of the dramatic toll of ZSD on caregivers and its impact on patients' care. Addressing the caregiver experience in ZSD is thus an urgent public health matter. More broadly, the study underscores the need for resources, networks and other support systems for caregivers of pediatric rare diseases. Despite the limited treatment options available for many rare pediatric diseases, simple, targeted resources for emotional support may greatly improve the lives of families dealing with rare diseases.

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## Conflicts of interest

Authors have no relevant conflicts of interests to disclose.

## Authors contributions

MB, MM, KMG & MBG — Conception and design.  
 MB, MM, DRS & RKC — Analysis and interpretation of data.  
 MB, MM, DRS, JBR, KMG & WBR — Drafting/revising the article.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgmr.2019.100459>.

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