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Retrospective Study

Clinical features, Diagnosis and Treatment Experience of Chinese 566 Patients with Peutz-Jeghers Syndrome

Clinical Features and experience of Chinese PJS patients

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Abstract

BACKGROUND

Peutz-Jeghers syndrome (PJS) is a clinically rare disease with pigmented spots on the lips and mucous membranes and extremities, scattered gastrointestinal polyps and susceptibility to tumors as clinical manifestations. Effective prevention and cure methods are still lacking. Here we summarize the clinical features and treatment experience of 566 Chinese patients with PJS from a Chinese medical center.

AIM

To explore the clinical features, diagnosis and treatment experience of Peutz-Jeghers syndrome (PJS) in a Chinese Center.

METHODS

The diagnosis and treatment information 566 cases of PJS admitted to the Air Force Medical Center from January 1994 to December 2022 are summarized. A clinical database was established covering age, gender, ethnicity, family history, first treatment age, time and sequence of appearance of mucocutaneous pigmentation, polyps distribution, polyps quantity and diameter, frequency of hospitalization, frequency of surgical operations, *etc*. The clinical data was retrospectively analyzed by using SPSS 26.0 software, with $P<0.05$ considered statistically significant.

RESULTS

55.3% males, 44.7% females; median time for the appearance of mucocutaneous pigmentation: 2 years; median time from the appearance of mucocutaneous pigmentation to the occurrence of abdominal symptoms: 10 years; 92.2% of patients undergo small bowel endoscopy and treatment, with 2.3% leading to serious complications. There was statistical significance between the number of enteroscopies and cancer (P = 0.004, Z=-2.882); 71.2% of patients underwent surgical operation, 75.6% of patients underwent surgical operation before the age of 35, and there was a

statistically significant difference between frequency of surgical operations and cancer (P = 0.000, Z=-5.127). At 40 years of age, the cumulative risk of intussusception in PJS was approximately 60.3%; at 50 years of age, the cumulative risk of intussusception in PJS was approximately 81.5%; at 50 years of age, the cumulative risk of cancer in PJS was approximately 49.3%; and at 60 years of age, the cumulative risk of cancer in PJS was approximately 71.7%.

CONCLUSION

The risk of intussusception and cancer of PJS polyps increases with age. PJS patients ≥ 10 years old should undergo annual enteroscopy. Endoscopic treatment has a good safety profile and can reduce the occurrence of polyps intussusception and cancer. Surgery should be conducted to protect the gastrointestinal system by removing polyps.

Key Words: Peutz-Jeghers syndrome; management; intussusception; canceration; STK11

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Core Tip: Peutz-Jeghers syndrome (PJS) is a clinically rare autosomal dominant inherited disease with pigmented spots on the lips and mucous membranes and extremities, scattered gastrointestinal polyps and susceptibility to tumors as clinical manifestations. Effective prevention and cure methods are still lacking. Here we summarize the clinical features and treatment experience of 566 Chinese patients with PJS from a Chinese medical center. To promote clinical understanding of Chinese PJS and improve clinical diagnosis and treatment ability.

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is clinically characterized by labial mucosa, extremity terminal pigmentation and gastrointestinal multiple hamartoma polyposis.[1-3] Mucocutaneous pigmentation generally does not require specific treatment, but PJS polyposis is clinically serious. Gastrointestinal polyps cause secondary rupture, bleeding, intussusception, intestinal obstruction, abdominal pain, abdominal distension, hematochezia and other symptoms, and their further development causes enteric necrosis, intestinal perforation and even cancer[4-7]. Therefore, it is necessary to summarize safe and effective treatments for PJS polyps. From January 1994 to October 2022, the Air Force Medical Center has diagnosed and treated 566 patients with PJS, thereby accumulating some clinical experience. This paper summarizes and analyzes such experience in order to explore the clinicopathological features, diagnosis and treatment experience in PJS from a Chinese medical center.

MATERIALS AND METHODS

1.1 Materials

Patients diagnosed with PJS (ICD-9, ICD-10 disease code Q85.801) from January 1994 to October 2022 in the Air Force Medical Center's electronic medical record system were screened according to the standard.[8, 9] Suspicious diagnoses and misdiagnoses were excluded, leaving a total of 566 patients. Statistical parameters: ①General information: gender, age, ethnicity, family history, *etc.*; ②Clinical information: occurrence age and location of mucocutaneous pigmentation, time from mucocutaneous pigmentation to the appearance of abdominal symptoms (such as abdominal pain, intestinal obstruction, gastrointestinal bleeding, *etc.*), polyps distribution, polyps burden and maximum diameter, polyps pathology and canceration *etc.*; ③ Diagnosis and treatment information: initial treatment age, follow-up age, frequency of hospitalization, frequency of surgical operations, frequency of endoscopy and comorbidities, *etc.* A database of clinical parameters was established and retrospective statistical analysis was performed.

1.2 Statistical analysis

SPSS 26.0 software was used for descriptive statistical analysis. A normal testing method was applied to evaluate the quantitative data, which was expressed as average ± standard deviation ($\bar{x} \pm sd$); T-test was used for comparisons between groups; skewed distribution data was described as medians (interquartile ranges); the Mann-Whitney U test was used for comparisons between groups; qualitative data was expressed as percentages; the comparison of proportion and correlation analysis was evaluated by the $\chi 2$ test; and $P<0.05$ was considered statistically significant.

RESULTS

2.1 General data (table 1)

Table 1 General data of 566 patients with PJS

2.2 Clinical data (table 2)

Table 2 clinical data of 566 patients with PJS

2.2.1 First treatment age:

407 patients (71.9%) received initial treatment before 20 years old; 513 patients (90.6%) received initial treatment before 30 years old; there was a statistically significant difference between the age of initial treatment and family history of PJS (P = 0.035, Z=-2.114); the age of initial treatment of patients with family history was later than that those without family history. There was no significant difference between first treatment age and gender (Z=-0.105, P = 0.310). There was no significant difference between first treatment age and blood group (H=1.652, P = 0.648). There was a significant statistical difference between first treatment age and malignant tumor (P = 0.009, Z=-2.631). The median age of patients with malignant tumors was significantly higher than that those without malignant tumors, which suggests that the later the age of initial treatment, the more likely the occurrence of malignancy.

2.2.2 Mucocutaneous pigmentation:

563 cases (99.5%) had mucocutaneous pigmentation, which appeared before 7 years old in 507 cases (90.1%). Mucocutaneous pigmentation sequence: 402 cases (71%) had mucocutaneous pigmentation on both the lips and limbs; 45 cases (8%) had

mucocutaneous pigmentation on the lips and then on the limbs; 4 cases (0.7%) had mucocutaneous pigmentation on the limbs and then on the lips; and 16 cases (2.8%) had mucocutaneous pigmentation in an unknown sequence. There was a statistically significant difference between the age of the appearance of mucocutaneous pigmentation age and family history (P = 0.016, Z=-2.415), and the age of the appearance of mucocutaneous pigmentation in cases with family history was significantly lower than that in those without family history. There was no significant difference in the age of the appearance of mucocutaneous pigmentation and gender (P = 0.686, Z=-0.404). There was no significant difference between the age of the appearance of mucocutaneous pigmentation with blood group (H=2.3, P = 0.512). The age of the appearance of mucocutaneous pigmentation was positively correlated with the age of initial treatment (r = 0.197, P = 0.000). The age of initial treatment was positively correlated with small intestinal polyps burden (r = 0.097, P = 0.034) and colorectal polyps burden (r = 0.208, P = 0.000), and negatively correlated with the maximum diameter of colorectal polyps (r=-0.120, P = 0.024).

2.2.3 Interval time between age of mucocutaneous pigmentation and occurrence of gastrointestinal symptoms:

529 cases (93.5%) had clear records, with 3 cases (0.5%) without gastrointestinal symptoms and 34 cases (6.0%) with missing data. The interval time was negatively correlated with the age of pigmentation (r=-0.175, P = 0.000). There was statistical significance between the interval time of gastrointestinal symptoms and colorectal polyps (χ2=0.03, P = 0.015). The greater the burden of colorectal polyps, the shorter the interval until the occurrence of gastrointestinal symptoms.

2.2.4 Gastrointestinal polyps:

PJS polyps were distributed in the stomach in 421 cases (74.4%), small intestine in 546 cases (96.5%) and colorectal in 445 cases (78.6%). There were 26 cases (4.6%) with gallbladder polyps, 4 cases (0.7%) with nasal polyps and 2 cases (0.35%) with uterine polyps. Pathological types: There were 433 cases of hamartoma, 75 cases of adenoma, 32 cases of canceration and 23 cases of hyperplastic and inflammatory polyps. There was

no statistically significant difference between the maximum diameter of gastric polyps and the maximum diameter of small intestinal polyps ($\chi 2=656.319$, $P = 0.991$). There was a statistically significant difference between the maximum diameter of gastric polyps and the maximum diameter of colorectal polyps ($\chi 2=639.396$, $P = 0.026$). There was a statistically significant difference between the diameters of small intestinal polyps and colorectal polyps ($\chi 2=1443.082$, $P = 0.000$). There was a statistically significant difference between the gastric polyps burden and small intestinal polyps burden ($\chi 2=1000.592$, $P = 0.000$). There was a statistically significant difference between the gastric polyps burden and colorectal polyps burden ($\chi 2=468.22$, $P = 0.000$). There was a statistically significant difference between the small intestinal polyps burden and colorectal polyps burden ($\chi 2=1739.598$, $P = 0.000$).

2.2.5 Endoscopic examination and treatment:

Among the 566 patients in this study, 522 (92.2%) underwent enteroscopy and treatment, and a total of 1,381 small intestinal enteroscopies were completed (841 transoral small intestinal enteroscopies and 533 transanal small intestinal enteroscopies). About 7236 polyps were found through endoscopy (1959 gastric polyps, 3555 small intestinal polyps and 1722 colorectal polyps). 346 polyps < 5 mm were not treated, 1489 polyps between 5~10 mm were electrocoagulated and removed by argon plasma coagulation (APC), 917 polyps between 10~20mm were removed by endoscopic mucosal resection (EMR) and snare polypectomy (SP), and 4484 polyps > 20 mm were removed by endoscopic mucosal dissection (ESD). After endoscopic treatment, 60 cases developed clinical symptoms (10 cases of abdominal discomfort, 35 cases of incomplete intestinal obstruction and 15 cases of gastrointestinal perforation and bleeding), and 47 cases (91.7%) were cured. However, 13 cases (2.3%) developed gastrointestinal perforation and bleeding, and accepted surgical operations for the perforation repair or partial resection of the small intestine. 329 patients (58.1%) underwent gastroscopy 673 times, 393 patients (69.4%) underwent colonoscopy 868 times, 38 patients (6.7%) underwent capsule endoscopy 41 times and 9 patients (1.6%) underwent gastroenterography examinations. There was a statistically significant difference

between the number of small intestinal enteroscopies and carcinogenesis (P = 0.004, Z=-2.882), which suggests that the greater number of follow-up enteroscopies, the easier the detection of polyps canceration.

2.3 Surgical operation treatment:

Laparotomy is the most common type of surgery for the treatment of PJS, in which multiple polyps in the gastrointestinal are treated with intraoperative endoscopic resection or small incision removal, and it is necessary to removal part of the bowel in some severe cases. Due to the progress of endoscopic techniques in the treatment of PJS, we advise removing all the polyps that can be reached at the same time. Current indications for surgery: ①the endoscope could not reach the lesion; ②the occurrence of acute intussusception and intestinal obstruction symptoms prevented endoscopic treatment; ③patients with sessile flat polyps, giant polyps or densely distributed polyps which are difficult to remove by endoscopy; ④polyps pathologically confirmed to have become malignant or highly suspected of canceration under endoscopic observation; ⑤the occurrence of perforation during endoscopic polyps resection or postoperative perforation which could not be treated conservatively; ⑥the occurrence of major bleeding occurred during or after endoscopic treatment which did not respond to conservative medical treatment; ⑦patients or their family members requested the disposable surgical removal of polyps. A total of 405 patients (71.6%) underwent 655 surgical procedures, 305 patients (75.6%) underwent abdominal surgery before the age of 35, 168 patients (29.7%) underwent more than 2 times operations and 1 patient underwent 7 times operations. These patients underwent nasopharyngeal polypectomy 1 time, subtotal gastrectomy 2 times, Partial small bowel resection 570 times, pancreaticoduodenectomy 7 times, partialcolectomy 22 times, left-semicolon resection operation 2 times, right hemicolectomy resection operation 4 times, pancolectomy 11 times, radical resection of small bowel cancer 18 times, radical operations for colon cancer 6 times, radical resection of rectal carcinoma 2 times, radical surgery for ovarian cancer 3 times, radical hysterectomy 3 times, radical resection of pulmonary carcinoma 3 times and modified radical mastectomy 1 time. There was a statistically significant

difference between the number of operations and carcinogenesis (P = 0.000, Z=-5.127), which suggests that patients with cancer require more surgery.

2.4 Drug therapy:

9 patients were treated after small intestinal enteroscopies with the oral administration of celecoxib capsules, 400 mg, 1/d; 3 patients developed allergic reactions 3 developed hematochezia, after which the treatment was ceased. 2 patients completed a 6-month course of treatment and 1 completed a 9-month course of treatment. The reexamination of small intestinal enteroscopies showed that only 1 case was effective. Traditional Chinese medicine (TCM) was used in 30 cases and was shown to inhibit some small polyps < 1cm, but its inhibitory effects on polyps ≥ 1cm were weak with an overall effective rate of only 40%.

2.5 Follow-up:

As of the deadline of this study, 361 patients were followed up on more than twice at our hospital, and no death occurred. 338 cases (189 males and 149 females with a median age of 27.5 years) had previously or concurrently developed intussusception, intestinal obstruction or intestinal perforation. The Kaplan-Meier method showed that, at the age of 40, the cumulative risk of intussusception in PJS patients could reach 72%, and at 50, the cumulative risk of intussusception could reach 89.6% (Figure 1). 46 patients had malignant tumors (27 males and 19 females with a median age of 36.5 years). There were 18 cases of small bowel cancer, 8 cases of colorectal cancer, 6 cases of duodenal cancer, 3 cases of ovarian cancer, 3 cases of cervical cancer, 3 cases of lung cancer, 2 cases of gastric cancer, 1 case of cholangiocarcinoma, 1 case of breast cancer and 1 case of nasopharyngeal cancer. Kaplan-Meier Survival analysis showed that, at the age of 50, the cumulative risk of cancer in PJS patients could reach 49.3%, and at 60, the cumulative risk of cancer could reach 71.7% (Figure 2).

DISCUSSION

This study found that 90.1% of PJS patients developed mucocutaneous pigmentation before the age of 7. The median time between the appearance of mucocutaneous

pigmentation and the occurrence of abdominal symptoms was 10 years. Therefore, as PJS patients are often outpatients undergoing dermatological and stomatological treatment for mucocutaneous pigmentation, which is easy for doctors unfamiliar with the disease to misdiagnose, and valuable early treatment opportunities may thus be missed, so clinicians should be more vigilant. PJS that does not cause the malignant transformation of mucocutaneous pigmentation on the lips and limbs generally does not need to be treated[10]. Some scholars used a 755 nm picosecond laser to treat mucocutaneous pigmentation on the lips, which showed a reduction in pigmentation of 50%~75% after 3 mo, and good recovery after surgery.[11]

At present, there is no effective treatment for PJS polyps. Some scholars used everolimus (mTOR inhibitor, a derivative of rapamycin) to treat 2 PJS patients, and the results showed that pancreatic cancer progressed after 2 mo in 1 patient, while the other refused to continue treatment after severe toxicity, so the trial was canceled[12]. One study [13] found that patients with PJS (2/6) responded well to celecoxib and had fewer gastric polyps, suggesting that COX-2 inhibitors may be beneficial in PJS therapy. However, in our study, celecoxib capsules were used to prevent polyps, and only 1 case was effective. This suggests that COX-2 inhibitors may not be ideal targets for PJS drug therapy, as they had a high proportion of side effects (6/9) such as allergic reaction and gastrointestinal bleeding. We also treated 30 PJS patients with TCM, which had an effective rate for small polyps of only 40%, while being basically ineffective for large polyps. This study showed that PJS polyps could be distributed in the stomach (74.4%), small intestine (96.5%) and colorectal (78.6%). The burden and diameter of small intestine polyps were much higher than those of stomach polyps, which was the root cause of intussusception and intestinal obstruction. We found that some PJS patients had concurrent gallbladder polyps, nasal polyps, cervical polyps, *etc.* Whether these are the extragastrointestinal manifestations of PJS polyps still needs to be supported by pathological evidence. Endoscopic treatment methods for PJS polyps include EMR and ESD.[[14, 15] Our study showed that the incidence of gastrointestinal bleeding, perforation and other serious complications during colonoscopy and endoscopic

treatment was 2.3%. Overall, the endoscopic treatment of PJS polyps is safe and feasible. Due to gastrointestinal polyps occurring in multiple places, patients often undergo multiple laparotomy operations, which can cause severe intraperitoneal adhesion. Laparoscopic surgery is difficult and not recommended as a routine treatment method for PJS. Laparoscopic surgery and small intestinal endoscopy surgery could be used for abdominal exploration or patients with moderate abdominal adhesions. Laparoscopic perforation repair or hemostatic suture can be used as adjuvant treatments for endoscopic complications when removal large localized polyps, dense intestinal segments of polyps with perforation or bleeding during endoscopic treatment.

Open surgery for PJS patients should be explored to determine the distribution of polyps in whole gastrointestinal tract. Following the principle of organ protection, it is recommended to perform intestinal adhesion release and try to avoid large sections of intestinal resection causing short bowel syndrome. Multiple small incisions can be made in the intestinal wall to remove all palpable polyps, but when encountering necrotic, perforated or dense bowel polyps, bowel segment resection is recommended. For patients diagnosed with malignant transformation, radical resection surgery and regional lymph node dissection surgery should be performed on cancerous intestinal segments.

PJS is a tumor-susceptible syndrome,[16-18] and it has been previously reported that PJS polyps have a development pathway with hamartoma-adenoma-cancer.[19] In our study, 46 cases were pathologically confirmed to have a malignant tumor, of which 35 cases (76.1%) were PJS polyps malignant transformation and the rest were breast cancer, cervical cancer, lung cancer, ovarian cancer, nasopharyngeal cancer and cholangiocarcinoma. This group showed that the cumulative cancer risk of PJS patients reached 49.3% at the age of 50 and 71.7% at the age of 60. Considering the short follow-up time of some cases, the actual cumulative risk of carcinogenesis may be higher. For PJS patients, we should also pay attention to their mental health, especially adolescent PJS patients. With the deepening of their understanding of the PJS disease, such as that it is a genetic disease which requires long-term hospitalization, they may gradually

develop the psychology of hating their parents and retaliating against society. We also found that PJS patients have different degrees of concern about the risk of cancer, which reminds us that we should strengthen psychological counseling and provide professional interpretation for PJS patients in clinical treatment in order to reduce their anxiety and depression, and where necessary, psychologists should be involved in the treatment process of PJS patients.

Our study showed that there was a statistically significant difference between the age of the occurrence of mucocutaneous pigmentation and family history (P = 0.016, Z=-2.415). As such, we suggest that suspected or already confirmed PJS patients should undergo Next Generation Sequencing (NGS), which can reliably quantify the incidence, penetrance, mutation type and expression of PJS. When adult patients are pregnant, they can receive preimplantation genetic testing (PGT) or preimplantation genetic screening (PGS) to predict whether there is a correlation with STK11 or other gene mutation.[20, 21] If screening finds that the fetus is a carrier of the STK11 gene mutation, then the parents can terminate the pregnancy; thus, this approach makes it possible to have healthy children.

At present, there is no unified protocol for the follow-up of PJS polyps. Our study showed that the occurrence time of mucocutaneous pigmentation in most patients is earlier than the occurrence time of gastrointestinal symptoms, which is a good window period in which to intervene in the development of polyps. We suggest that PJS patients should start endoscopic examinations when they are 10 years old, and the endoscopic treatment of gastrointestinal polyps ≥10 mm in diameter should be performed to prevent intussusception and intestinal obstruction. The whole gastrointestinal tract should be explored by oral and transanal small intestinal enteroscopy as far as possible. Cold forceps polypectomy and cold snare polypectomy or APC can be used on polyps < 10mm which are sessile or flat; combined with high-frequency electroresection, effective eradication can be achieved without complications such as bleeding and perforation. If small intestinal enteroscopy exploration finds moderate intussusception, incomplete intestinal obstruction and a perforation area < 1cm, then conservative treatment

methods can be used such as fasting, fluid infusion, gastrointestinal decompression, endoscopic balloon reduction or perforation repair with titanium clips. If polyps ≥ 10 mm are detected, EMR or ESD will be required to remove them, but the possibility of perforation should be noted. Early surgical treatment should be performed for irretrievable intussusception, complete intestinal obstruction, intestinal perforation area ≥ 1 cm, malignant polyps and failure of conservative treatment. PJS patients < 10 years old may undergo noninvasive examinations such as abdominal ultrasound, CT, capsule endoscopy, gastrointestinal contrast or MR to assess the burden and diameter of their gastrointestinal polyps. If polyps < 10 mm are found, resection can be attempted for a smaller quantity of polyps, but if they cannot be removed, a biopsy will be required to determine the pathology of the polyps and estimate the next follow-up time, and the growth rate of the polyps will need to be closely monitored. For giant polyps, multiple endoscopic resections should be carried out, but for diffuse distributions of polyps, the complete resection of all polyps in the entire intestinal canal should not be excessively pursued in order to prevent short bowel syndrome, and the patients should be monitored every 1 to 2 years.

CONCLUSION

The development of gastrointestinal symptoms in PJS patients is closely related to the age of the appearance of mucocutaneous pigmentation and polyps burden and diameter. The later the age of mucocutaneous pigmentation, the more severe the gastrointestinal symptoms, and patients receive more frequent operations and hospitalization. As PJS polyps have a high risk of intussusception and carcinogenesis, patients aged ≥ 10 years should undergo a small intestinal enteroscopy every 1–2 years. Endoscopic treatment has a good safety profile and can have significant beneficial effects for PJS patients, and timely endoscopic treatment can reduce the risk of the intussusception and carcinogenesis of polyps.

ARTICLE HIGHLIGHTS

Research background

Peutz-Jeghers syndrome (PJS) is a clinically rare autosomal dominant inherited disease with pigmented spots on the lips and mucous membranes and extremities, scattered gastrointestinal polyps and susceptibility to tumors as clinical manifestations. Effective prevention and cure methods are still lacking.

Research motivation

Here we summarize the clinical features and treatment experience of 566 Chinese patients with PJS from a Chinese medical center. To promote clinical understanding of PJS and improve clinical diagnosis and treatment ability.

Research objectives

To explore the clinical features, diagnosis and treatment experience of PJS in a Chinese Center.

Research methods

The clinical data of 566 PJS cases admitted to the Air Force Medical Center from January 1994 to December 2022 was retrospectively analyzed covering age, gender, ethnicity, family history, first treatment age, time and sequence of appearance of mucocutaneous pigmentation, polyps distribution, polyps quantity and diameter, frequency of hospitalization, frequency of surgical operations, *etc.*

Research results

55.3% males, 44.7% females; median time for the appearance of mucocutaneous pigmentation: 2 years; median time from the appearance of mucocutaneous pigmentation to the occurrence of abdominal symptoms: 10 years; 92.2% of patients undergo small bowel endoscopy and treatment, with 2.3% leading to serious complications. There was statistical significance between the number of enteroscopies and cancer ; 71.2% of patients underwent surgical operation, 75.6% of patients

underwent surgical operation before the age of 35, and there was a statistically significant difference between frequency of surgical operations and cancer . At 40 years of age, the cumulative risk of intussusception in PJS was approximately 72%; at 50 years of age, the cumulative risk of intussusception in PJS was approximately 89.6%; at 50 years of age, the cumulative risk of cancer in PJS was approximately 49.3%; and at 60 years of age, the cumulative risk of cancer in PJS was approximately 71.7%.

Research conclusions

The risk of intussusception and cancer of PJS polyps increases with age. PJS patients ≥ 10 years old should undergo annual enteroscopy. Endoscopic treatment has a good safety profile and can reduce the occurrence of polyps intussusception and cancer. Surgery should be conducted to protect the gastrointestinal system by removing polyps.

Research perspectives

The clinical data of 566 PJS cases diagnosed and treated by a Chinese medical center were retrospectively analyzed, and the clinical characteristics and diagnosis and treatment process of Chinese PJS were summarized.

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